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Editorial

"THE FREQUENCY DISTRIBUTION OF EPISODES OF RHEUMATOID ARTHRITIS AS SHOWN BY PERIODIC EXAMINATION," BY BEALL AND COBB

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THE paper by Beall and Cobb in the current issue of the JOURNAL OF CHRONIC DISEASES is a major contribution to the epidemiology of rheumatic disease, and chronic disease in general.

First, it makes quite clear what previous studies by Cobb and his associates at the University of Pittsburgh School of Public Health have suggested: One cannot divide the population into those suffering from rheumatoid arthritis and those not suffering from it. The disease process occurs as a continuum of disturbance, not as a have-it or don't-have-it phenomenon. Both clinicians and epidemiologists have tended to base their studies of rheumatoid arthritis, as well as other diseases, on the "definition of a case" whereby they classify the population into those having the disease and those not having it. This pattern of thought probably arose from experience with acute infectious disease. However, it fails to satisfy the need in studies of rheumatoid arthritis and other chronic diseases in which we must deal not just with the question of presence or absence, but also with the questions of how much and when episodes of the disease occur.

Second, the authors have applied and elucidated a mathematical scheme for studying the questions, how much and when, in reference to rheumatoid arthritis. The same general scheme obviously can be and should be applied to other chronic diseases, especially where clear-cut methods of measurement are available, for example, arterial hypertension, diabetes mellitus, and glaucoma. It will also be applicable to chronic conditions where measurement is still crude, for example, multiple sclerosis, alcoholism, and breast cancer. In all of these and other chronic diseases in which periodicity and variable progressiveness appear so important, the general method of investigation and analysis presented by Beall and Cobb

should greatly assist understanding of the disease processes. Morris[1] calls this use of epidemiology, "completing the clinical picture."

Finally, by indicating how to classify a population with reference to how much and when a disease affects the members of the population, the authors provide a means for studying epidemiologically the quantitative aspects of disease occurrence. Thus one can analyze the presence or absence of characteristics (pregnancy, infection, mental stress, cold, etc.) that might affect occurrence of the disease, not in relation to "cases" and "noncases" of rheumatoid arthritis, but rather the relationship of these characteristics to the severity and periodicity of the disease. The latter type of analysis may be crucial to understanding the many chronic diseases with exacerbations and remissions of measurable departure from the normal or nondisease physiological state.

The authors use of the term, exciting, is appropriate.

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THE FREQUENCY DISTRIBUTION OF EPISODES OF RHEUMATOID ARTHRITIS AS SHOWN BY PERIODIC EXAMINATION

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THE remittent nature of rheumatoid arthritis is well known. This presents a serious problem when one desires to describe a population with respect to the frequency of this disease, for the usual procedure is to count the number of persons affected at a given point in time. If one finds 10 per cent of persons affected, this may mean that there are in the population 10 per cent who are continuously affected or 100 per cent who are each affected one-tenth of the time or any other appropriate combination which would yield a probability of 10 per cent of individuals being found in an episode of activity. A method is, therefore, needed to form estimates of the frequency of individuals according to the part of their time spent in episode. It is to this problem that we address ourselves here.

In the extreme imaginary contrast above, the results would be essentially the same on a first examination of the population. An immediate discrimination would, however, be made on a second examination. In the situation with 10 per cent chronic cases, all necessarily discovered at a first examination, there would be found no additional cases on the second examination. On the other hand, in the situation where everyone spent one-tenth of his time in episode, a second examination would tend to pick up almost as many new cases as the first examination. Long-continued periodic examination would, in this second situation, pick up more and more cases.

The real situations must, of course, tend to be mixtures of chronic cases and intermittent cases. At the first examination one must discover all chronic cases, and in addition a few which are only occasionally in episode but do happen to be so at the time of the first examination. At a second examination futher cases will be picked up of men occasionally in episode. Long-continued observation will, of course, always be rewarded by cases at least occasionally in episode.

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We have been particularly encouraged in our pursuit of this problem by the discovery that the essential data for such situations are given by an initial examination and a single follow-up examination. The main body of our discussion is written in terms of such a two-examination structure, though in practice more examinations may be desirable. The details of the basic structure on which our operation is built are set forth in Statistical Appendix C.

FIELD METHODS

A group of 331 employed male craftsmen and their foremen were screened monthly for manifestations of arthritis by a nurse who was especially trained for the project. The routine screening procedure, the results of which were recorded directly on IBM mark sense cards, included a question about morning stiffness and the results of a rapid routine examination of the peripheral joints plus the shoulders for pain on motion, tenderness, and swelling. A joint was recorded as swollen when any degree of definite capsular thickening with or without fluid could be demonstrated. In addition, during part of the study the men were asked to estimate the number of days during the preceding month on which they had suffered with swelling of the joints.

Of the 331 men, 274 were screened each month. The others missed one or more months for various reasons, from illness and death to termination of employment or transfer to a distant part of the plant. The 57 men on whom the data are incomplete have been compared on 71 social and medical variables with the 274 who remained under continuous observation and were found to be significantly different with respect to only one. This variable was the medical classification "fit for limited duty only." As might be expected, the persons who are something less than fully healthy lost more time from work than their colleagues and, therefore, had a greater chance of being unavailable to be screened. There was no undue proportion of persons with evidence of arthritis in this group.

In order to test the reliability of the nurse's observations, all persons found by her to have joint swelling were checked by a physician on the occasion of the first such finding, and most of the men were screened within a week of their annual physical examination so comparative data are available. These are presented in Table I. The degree of agreement is, in our opinion, about as good as one would get between two physicians. In fact, it is substantially better than the agreement that one obtains between physicians in some other fields, e.g., cyanosis,[5] pulmonary emphysema,[7] finger clubbing,[10] and liver size.[11]

In the course of supervising the nurse and in the examination of the data, there arose a small suspicion that her criteria did not become stabilized for a couple of months. To be on the safe side, therefore, the analyses that follow are confined to the fifth through the sixteenth month of the study (January through December, 1958).

JOINT SWELLING

The type of fundamental data for our study may be illustrated by considering in some detail the manifestation of joint swelling among the 274 men available.

TABLE I. EXTENT OF AGREEMENT BETWEEN PHYSICIAN AND NURSE WITH REGARD TO THE PRESENCE OR ABSENCE OF JOINT SWELLING IN PATIENTS WHOM THEY EXAMINED WITHIN EIGHT DAYS OF EACH OTHER

NURSE	PHYSICIAN		TOTAL
	NO	YES	
No	208	16	224
Yes	29	69	98
Total	237	85	322

This manifestation is distinct from the others studied in that we have evidence on it in two forms. First, we have the occurrence of swelling at the time of the periodic examinations by the nurse, as we have for the other phenomena to be discussed later. Second, we have here, in addition, statements by the men as to the time of onset of swelling and its duration. These latter data are somewhat dubious but of interest because of their directness. We shall consider them first and then go on to data in the periodic form which are more characteristic of our study.

The body of records on the number of days that the subjects said that they had spent in an episode of swelling were recorded for a period of 304 days (March through December, 1958). By virtue of their historical nature, the data must be inferior to the objective observations made once each month. However, consideration of them illustrates the manner in which we should think about the present problem. From the records of reported time in episode of swelling we calculated the fraction of time (of a total of 304 days) spent in episode. These data have been classified in Table II. The classification of the 190 men who spent a fraction of their time, which may be called p, between 0.0000 and 0.0030 in episode (i.e., less than one of the 304 days) is actually the group which reported no days in episode. The contribution of this class toward total time in episode is trivial.

The data in Table II are presented in the histogram of Fig. 1, which is in two parts, *A*, for the entire range of p, and *B*, for the range from below 0.01 up to 0.14. In these two parts the scale had to be made very different in order to show anything. As can be seen, a smooth fit is shown. Explanation of the means by which it was obtained follows, and is given in more detail in Appendix C. The frequency distribution involved, either as a histogram or as a smooth function, is a difficult one in that it starts very high (at infinity for the smooth fit) and then drops to a comparatively low level. In the present case there is a small upturn on the right. A frequency distribution of this form may somewhat dismay readers who have not encountered it before, for we are most used to the type of distribution which starts at practically zero on the left, comes to a maximum, and declines to practically zero on the right. The fundamental concepts of the familiar case are, however, sufficient to deal with the present one. In the first instance, it embraces an area of unity, which means that everyone spends some fraction of his time, p, from 0.0 to 1.0 in episode. In order to find the part of

TABLE II. TIME IN EPISODE OF SWELLING BY CLASSES

FRACTION OF TIME IN EPISODE	PROBABILITY (MIDPOINT) OF FINDING IN EPISODE	FREQUENCY
0.0000 to 0.0030	0.0015	190
0.0030 to 0.0060	0.0045	10
0.0060 to 0.0150	0.0105	9
0.0150 to 0.0300	0.0225	11
0.0300 to 0.0600	0.0450	10
0.0600 to 0.1400	0.1000	10
0.1400 to 0.2200	0.1800	5
0.2200 to 0.3000	0.2600	7
0.3000 to 0.3800	0.3400	3
0.3800 to 0.4600	0.4200	6
0.4600 to 0.5400	0.5000	2
0.5400 to 0.6200	0.5800	0
0.6200 to 0.7000	0.6600	3
0.7000 to 0.7800	0.7400	1
0.7800 to 0.8600	0.8200	0
0.8600 to 0.9400	0.9000	2
0.9400 to 1.0000	0.9700	5
		274

the population which spends a given fraction of its time in episode, the appropriate integral of the distribution is required. For a rough instance, men spending from 0.6 to 0.9 of their time in episode have the frequency distribution at a height of about 0.1 (Fig. 1,*A*). Therefore, roughly, a part of the men, $(0.9 - 0.6) \times (0.1) = 3\%$, so spend their time. Our later discussion, which is largely concerned with smooth fits, will be systematically translated back into such statements as to the part of the population spending broad fractions of its time in episode.

It is possible to calculate, as in Appendix C, from the data of Table II the number of cases of swelling to be expected from a first examination, E_1, (18.8), and the additional number to be expected on a second examination, E_2, (7.8). These values will be compared below with the empirical values. For the moment, however, they are of particular interest as the necessary and sufficient basis for fitting the smooth function shown in Fig. 1.

The procedure of fitting that is employed is based on these values, E_1, E_2, and N, the total number of individuals examined. From them we calculate five values, m_1, m_2, A_1, A_2, and y_e, as given in Appendix C, Equations (1) through (3). These five values are employed, as in Equation (4), to provide smooth functions of the type previously shown in Fig. 1 and subsequently shown in Fig. 2.

It may surprise the reader, for it certainly surprised us, that as little information as that from two examinations is all that is required to specify the frequency distribution of fraction of time in episode in a population. Such economy arises from a first assumption that the general form and limits of the distribution may be assumed. The form is that of a Type I distribution. The limits are assumed to be that p may vary from 0.0 to 1.0.

Before we leave the subject of the frequency distribution of swelling according to the estimates of the subjects, there is a crucial question of direct medical importance. This is, are there two types of subjects—rheumatoid individuals,

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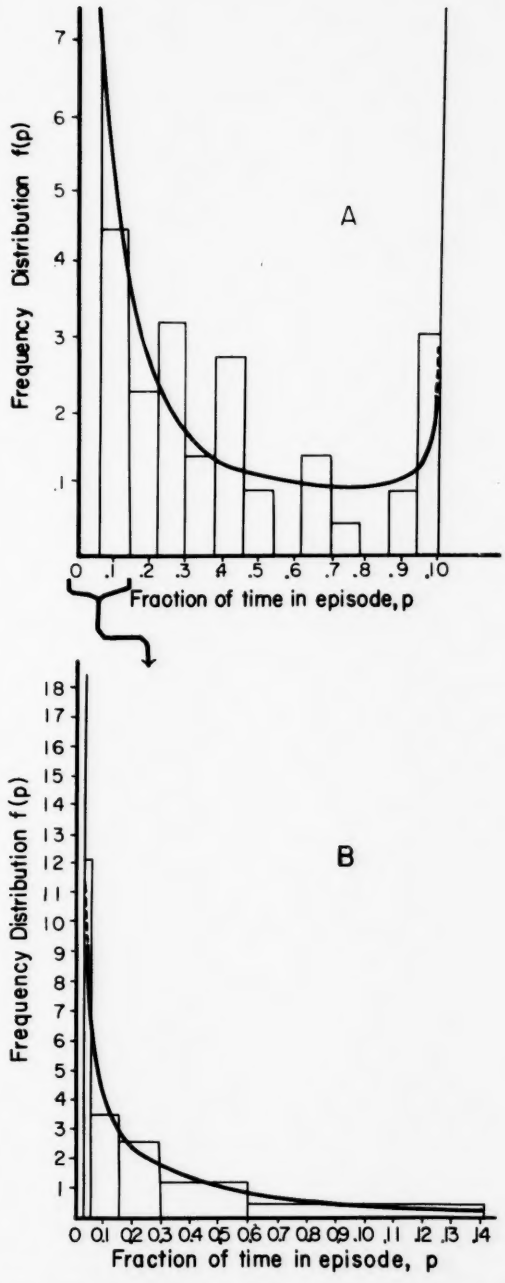
Frequency Distribution f(p)
A
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 .10
Fraction of time in episode, p
Frequency Distribution f(p)
B
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 .10 .11 .12 .13 .14
Fraction of time in episode, p

Fig. 1.—Frequency of episodes according to the fraction of time the individuals spend in episode of swelling according to their own estimates.

who show arthritic symptoms at least fairly frequently, and nonrheumatoid, who never show them—or is there, contrariwise, a continuum of affliction? The

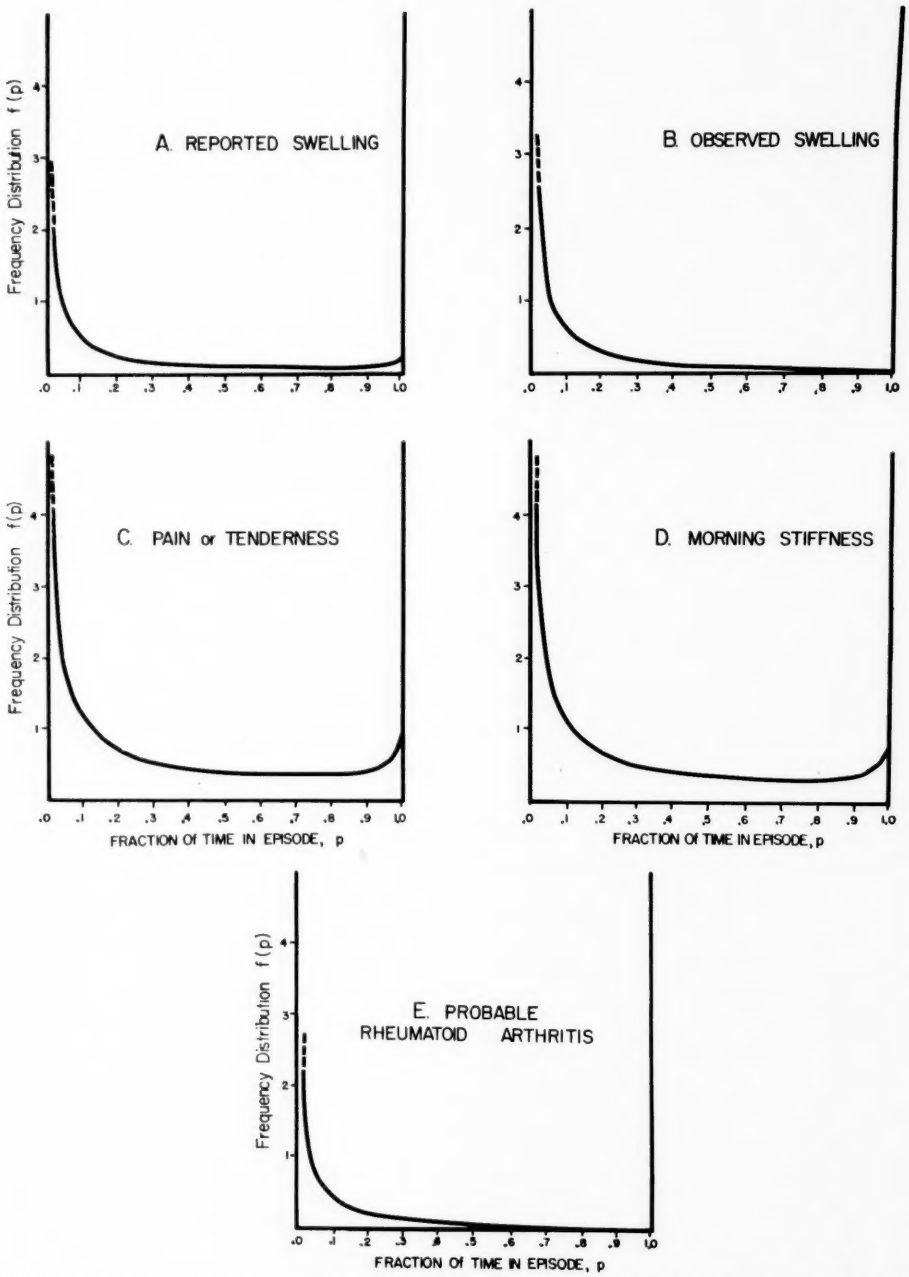

Fig. 2.—Frequency of episodes according to the fraction of time the individuals spend in episode of various kinds.

simple evidence in Table II or Fig. 1 answers that there is a continuum of affliction. Additional evidence supporting this point will be presented elsewhere.

The preceding data on time in episode of swelling have been presented to provide everyone with a fair and reasonable picture of the character of this phenomenon, but we must now turn to the more limited data that are commonly available in studying the symptoms of rheumatoid arthritis. This may be the number of instances seen at a preliminary examination and the number of further instances disclosed by subsequent examinations. For our purposes it transpires that a single subsequent examination is sufficient. For the year 1958 we also have available data of the more limited character: the number E_1 of instances of swelling on first examination was 13.667. This number is derived by a process of averaging, which is given in Appendix A. The number E_2 of further instances disclosed by a second examination 3 months later was 7.333 (of a similar average character). It will be remarked that the value of E_1 is appreciably lower than that of 18.8 which would have been anticipated from the men's subjective estimates of fraction of time in episode. Such discrepancy could arise from the subjects with swelling falsely overestimating the duration of their episodes. In any case, it is possible to calculate from the actual data where E_1 is 13.667 and E_2 is 7.333, the smooth function shown in Fig. 2,*B*. Fig. 2,*A*, which is Fig. 1,*A* in reduced form, is presented to facilitate comparison with Fig. 2,*B*.

The differences and the resemblances in Fig. 2, *A* and *B* may be most readily seen by converting from the smooth curve to integrals by broad classes. That is, the fractions of the area under the smooth curves should be found as is done in Table III. The algebraic detail of this procedure is given in Appendix C. Consideration of Table III shows that the distribution of episodes of swelling is substantially the same from the subjects' estimates and from objective periodic examination. The latter, however, shows low time in episode more common and high time in episode less common than the men report. Whether Table III or Fig. 2,*A* and *B*, is considered, it will be observed that the terminal upturn of the distribution, which was obtained from the men's reports, is lacking in the fit made on the basis of two examinations. This is to say that there is a comparatively numerous group that reports suffering from swollen joints all or almost all the time, but we should say that, from the data of objective periodic examinations, this group is a good deal smaller. Too much should not be made of this point because it could be only a small artifact of the process of fitting.

The emerging fact is that the two methods agree that some 10 per cent of this group of employed males spends 20 per cent or more of the time with clinically discernible joint swelling. To those directly involved in the field work this comes as no surprise, but to the consulting rheumatologist, who quite naturally assumes that joint swelling is a cause for a visit to the doctor, this may seem quite shocking. The reason for the shock is easily found in Table IV in which the frequency of reported visits to the doctor for arthritis is displayed in relation to the proportion of time in episode of swelling. It is clear that unless a man spends a large part of his time with active disease, he runs a relatively small chance of having his disease under observation by a member of the medical profession.

PAIN ON MOTION OR TENDERNESS, MORNING STIFFNESS, AND PROBABLE RHEUMATOID ARTHRITIS

For the manifestations, pain on motion, tenderness, and morning stiffness,

TABLE III. PARTS OF POPULATION SPENDING GIVEN FRACTIONS OF TIME IN EPISODE OF SWELLING ON BASIS OF THEIR ESTIMATE AND ON BASIS OF PERIODIC EXAMINATION

FRACTION OF TIME IN EPISODE	BASIS OF THEIR ESTIMATE (%)	BASIS OF PERIODIC EXAMINATION (%)
0.00 to 0.10	85.9	87.8
0.10 to 0.20	3.5	3.9
0.20 to 0.30	2.2	2.3
0.30 to 0.40	1.6	1.6
0.40 to 0.50	1.3	1.2
0.50 to 0.60	1.2	1.0
0.60 to 0.70	1.1	0.8
0.70 to 0.80	1.0	0.6
0.80 to 0.90	1.0	0.5
0.90 to 1.00	1.3	0.3

TABLE IV. VISITS TO PHYSICIAN FOR "TROUBLE WITH JOINTS OR BACK" ACCORDING TO PER CENT OF TIME SPENT WITH ONE OR MORE JOINTS SWOLLEN

TIME WITH JOINT SWELLING (%)	NO. OF MEN	EVER SEEN BY PHYSICIAN		SEEN BY PHYSICIAN IN PAST YEAR		VISITS TO PHYSICIAN IN PAST YEAR	
		NO.	%	NO.	%	NO.	PER MAN
85 to 100	7	7	100	4	56	39	5.5
1 to 85	76	36	47	16	21	94	1.2
<1	190	61	32	21	11	78	0.4
No information	1	0	0	0	0	0	—
Total	274	104	38	41	15	211	0.8

we have data on the number of cases at first examination and further cases on second examination 3 months later (Table V). The column headed "probable rheumatoid arthritis" gives similar evidence on the number of persons who, at the first and second examinations, were observed to have all three of the manifestations simultaneously. These three symptoms, plus consideration of their duration, form the most common basis for a diagnosis of probable rheumatoid arthritis according to the criteria of the American Rheumatism Association.[12] Since our present purpose concerns time in episode, the duration criterion is omitted.

Our object now is to calculate from the two examinations (the values E_1 and E_2) the frequency with which men spend various fractions of their time in episode. We must find something like Fig. 1 from periodic ascertainment of the occurrence of some symptoms like pain on motion or tenderness. For each situation the values, m_1, m_2, A_1, A_2, and y_e, are calculated, as shown in Appendix C, Equations (1), (2), and (3), and are added to Table V. The additions have been made so that anyone trying to refit Equation (4) for a Type I curve can see explicitly what values were derived from E_1 and E_2 and used. The curves in Fig. 2 show the distribution of fraction of time in episode for the various

considerations. This is the main immediate practical result of our endeavors. It may be observed that the function has not been plotted in quite so much detail in the latter cases as in our earlier case of Fig. 1, because the range of p has not been broken into two parts. It will be noted that the results previously shown in Fig. 1 are repeated in Fig. 2,*A* on a new scale, the same as that for the other symptoms, so that reported swelling may be compared with the other symptoms. In order that these results may be appreciated in a practical way, we have prepared Table VI which shows the parts of the population spending given fractions of their time in episode of various kinds. This table resembles Table III. The detail of the integration is given in Appendix C.

THE ACCUMULATION OF CASES WITH CONTINUED EXAMINATION

From the frequency distributions that have been found, it is possible to anticipate how many further cases would be expected if the examinations were continued at 3 month intervals. These anticipations can be contrasted with the results actually obtained at the third and fourth examinations. If we employ Equation (13) of Appendix C, it is possible to construct Table VII. There the empirical values of E_3 and E_4, which were available with low accuracy, are

TABLE V. MEAN NUMBER OF CASES AT FIRST EXAMINATION (E_1) AND MEAN INCREMENT AFTER 3 MONTHS (E_2) FOR SYMPTOMS (N = 274)

	OBSERVED SWELLING	PAIN OR TENDERNESS	MORNING STIFFNESS	PROBABLE RHUEMATOID ARTHRITIS
E_1	13.667	62.500	61.250	11.500
E_2	7.333	22.667	22.667	6.111
m_1	−0.935,279	−0.797,852	−0.796,440	−0.947,722
m_2	+0.232,852	−0.315,931	−0.292,939	+0.193,300
A_1	0.049,878	0.228,102	0.223,540	0.041,971
A_2	0.950,122	0.771,898	0.776,460	0.958,029
y_e	1.077,871	0.634,147	0.649,248	1.061,505

TABLE VI. PARTS OF POPULATION SPENDING GIVEN FRACTIONS OF TIME IN EPISODE FOR VARIOUS CONSIDERATIONS, ON BASIS OF PERIODIC EXAMINATION

FRACTION OF TIME IN EPISODE	OBSERVED SWELLING (%)	PAIN OR TENDERNESS (%)	MORNING STIFFNESS (%)	PROBABLE RHEUMATOID ARTHRITIS (%)
0.00 to 0.10	87.8	56.1	56.5	89.8
0.10 to 0.20	3.9	8.8	8.9	3.2
0.20 to 0.30	2.3	6.0	6.1	1.9
0.30 to 0.40	1.6	4.8	4.8	1.3
0.40 to 0.50	1.2	4.1	4.1	1.0
0.50 to 0.60	1.0	3.7	3.7	0.8
0.60 to 0.70	0.8	3.5	3.5	0.7
0.70 to 0.80	0.6	3.5	3.5	0.5
0.80 to 0.90	0.5	3.8	3.7	0.4
0.90 to 1.00	0.3	5.6	5.3	0.3

TABLE VII. FURTHER CASES OBSERVED AND TO BE EXPECTED WITH EXAMINATIONS AFTER THE SECOND

	OBSERVED SWELLING		PAIN OR TENDERNESS		MORNING STIFFNESS		PROBABLE RHEUMATOID ARTHRITIS	
	OBSERVED	EXPECTED	OBSERVED	EXPECTED	OBSERVED	EXPECTED	OBSERVED	EXPECTED
E_3	4.67	4.97	16.83	13.23	18.00	13.29	4.00	4.13
E_4	4.33	3.74	15.00	9.13	13.67	9.20	2.67	3.11
E_5	——	2.98	——	6.89	——	6.95	——	2.48

contrasted with the calculated values, $\hat{E}_3$ and $\hat{E}_4$. The correspondence seems reasonably good. In a broad way, our theory anticipated a continuing increment of about the magnitude that actually occurred. It is interesting that $\hat{E}_3$ and $\hat{E}_4$ seem a little low for pain on motion, tenderness, and morning stiffness because these are precisely the phenomena for which the period of 3 months was perhaps a little too short. The suggestion, as discussed in Appendix B, is that by a 6 months' interval between examinations the value of E_2 would be a little higher than at 3 months. It is plain in Equation (13) that with E_2 increased and E_1 unchanged, E_3 will increase. There is another possible explanation for the highness of empirical E_3 and E_4 in contrast to $\hat{E}_3$ and $\hat{E}_4$ in the case of pain on motion or tenderness, namely, there is a second phenomenon of pain arising from nonarthritic considerations, such as small sprains, which would contribute a steady and continuing increment with repeated examination. Statistically, such a phenomenon on any significant scale would probably mean that the Type I functions of Fig. 2 would become inadequate.

The results of Table VII give some reassurance as to the adequacy of the frequency distributions against p that were presented in the preceding section for the same symptoms. Those functions anticipate increments at third and fourth examinations of the magnitude actually observed. In a practical way, this increases our confidence that, for these symptoms which could not be investigated directly, there is again a continuum of affliction rather than two distinct classes of rheumatoid and nonrheumatoid arthritis.

DISCUSSION

The first question that arises in thinking about this direct mathematical approach to the problem of the remittancy of rheumatoid arthritis is: Are we really dealing with this disease, or are the manifestations discussed here too commonly due to other causes to be relevant? It is clear to us that the considerations studied here are relevant for rheumatoid arthritis for a number of reasons. These reasons can be stated only briefly here, but will be dealt with in detail in forthcoming publications. First, the manifestations considered form the basis of the criteria of the American Rheumatism Association for the diagnosis of rheumatoid arthritis. Second, we have actually studied in individuals the relationship between the fraction of time in episode of swelling and the final diagnosis

of rheumatoid arthritis. The results of this study indicate a strong association between the time in episode of swelling and the probability of diagnosis of rheumatoid disease.[9] Third, it is our epidemiologic impression that in this situation all the other causes of pain and swelling, except trauma, are so rare as to be negligible. We have excluded trauma from this study. This is consistent with the view that most of what is commonly called osteoarthritis is really a mixture of mild rheumatoid arthritis and degenerative changes in the joints.[3] Fourth, careful examination of the natural history of this disease indicates that it is usual for those who show severe symptoms to begin with only very mild manifestations which are indistinguishable from those discussed here.[4,13] Fifth, we now have serologic evidence that the group with mild symptoms resembles the group with severe rheumatoid arthritis, the only difference being in the quantity of the rheumatoid factor present.[1]

The continuity, or the lack of discontinuity, in these curves has been emphasized above. It is perhaps wise to be cautious and recognize that small discontinuities may not be perceived with the quantity of data available. However, in view of the data presented, it seems highly unlikely that the true picture should be the "either present or not" picture of hemophilia, for example. This does not mean that a hereditary factor is excluded; it merely suggests that, if genes are of any great importance in the pattern of causation, there must be involvement of multiple alleles, for a strong effect from a single allele would presumably have shown itself as a substantial discontinuity of the curves presented above.

The second point about the continuous gradient is that it argues against the old-fashioned notion of separating the population into those with no arthritis, those with fibromyositis with a benign prognosis, and those with rheumatoid arthritis who have a relatively poor prognosis. It suggests, instead, that all degrees of severity exist from the most extensive, continuously active case through moderate and mild intermittent disease, down to the individual who has rare attacks of morning stiffness. This is more in line with the majority of other disease processes, for, with the exception of genetically determined disease and human rabies which is almost uniformly fatal, one is hard put to it to name a competently studied disease that does not have a continuous gradient of severity.

So far, attention has been focused on description of some recently collected data. It is appropriate to turn for a moment to the applicability of this analytical method to future studies. First, we would like to emphasize that the notion of getting sufficient data from two examinations is valid only when the function is assumed. Since the applicability of Pearson's Type I curve should be studied further, more than two observations should be made in some future studies.

With regard to the interval between examinations it is important to remember that, if it is not taken into account, the seasonal pattern of the disease could have profound effects on the results. We have coped with this by the process of averaging, as shown in Appendix A. Beyond the seasonal problem, one must steer a middle course between an interval so short that the majority of episodes have not been terminated and a period so long that brand new onsets begin to interfere. It may be that examination at annual intervals, as suggested in Appendix B, is the most appropriate solution.

To us, it is quite exciting to think that it will now be possible to elucidate further the differences between populations. For example, we now have a method for examining the observed difference in point prevalence of rheumatoid arthritis between Pittsburgh, Pennsylvania, and Leigh, Lancashire, England,[2] to see if it is due to a different shape of the curve displaying the frequency distribution of persons according to proportion of time in episode, to a greater over-all frequency of affected persons, or to a combination of these. Such distinctions were mentioned in our introductory remarks. From now on all geographic studies of this disease should attempt to give the distribution of time in episode, for, intuitively, we believe that more will be learned about significant factors in the disease when we can discriminate in this fashion.

We cannot close without at least mentioning that this general approach is clearly valid for other remittent diseases.

SUMMARY AND CONCLUSIONS

1. From observations made monthly on a group of 274 employed men the severity gradient of rheumatoid arthritis among them has been described in terms of the part of their time that they spend with active disease. This frequency distribution is reasonably well represented by a Pearson Type I function.

2. The Type I frequency distribution can be found from an initial determination of whether a man is in episode, plus a subsequent redetermination for each man not then in episode.

3. The method developed provides a simple approach to making comparisons of the frequency of rheumatoid arthritis between groups in such a way as to eliminate the uncertainties arising from simple point prevalence measurements. Essentially, the procedure we recommend suggests that the usual point prevalence survey be supplemented by at least one additional examination to see how many additional afflicted persons are found. The second examination is curiously productive in that the two examinations are sufficient to specify the entire situation, if one is satisfied to assume the Type I distribution. Further examinations make it possible to check this point.

4. From the point of view of immediate results, we have a new view of rheumatoid arthritis as a very common disease that is only occasionally disabling. This position is supported by both data and theory which show how many cases with symptoms of rheumatoid arthritis will be disclosed by long-continued examination.

5. The evidence of these several rheumatoid manifestations suggests that the older notion of a distinct separation between rheumatoid arthritis and fibrositis is probably unwarranted; the continuity of affliction dispels this. The notion now must be that we are dealing with a single continuous gradient of disease from no involvement to severe involvement.

6. The mathematical techniques presented are presumably applicable to the study of other remittent diseases.

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APPENDIX A

Procedure Employed on Present Oak Ridge Data to Find Mean Number of New Cases per Examination

The preceding discussion has been based on statements as to the number of new cases per examination at intervals of 3 months. As pointed out in the text, the data used were for the last 12 of the 16 months of the investigation. The procedure for finding the number of cases at a first examination was to average the number of cases seen at the monthly examination, as if the study had actually been started each month. The results can be seen in the first examination line of Table VIII on "observed swelling" where the mean is 13.667. For the second examination 3 months later (Table VIII), the number of new cases is shown and averaged. The start is assumed to be in successive months. The basic month is changed as far as possible. By averaging all these quarterly increments, a value of 7.333 for the mean number of new cases after 3 months is obtained. For the third examination result (6 months after the start), the number of new cases seen averaged 4.667. As can be seen in Table VIII, the number of observations gets smaller as the time from start gets longer.

It should not be supposed that we recommend the procedure in Table VIII, for it was necessitated by the situation. Our present procedure of repeated examination of a fairly small body of men at fixed intervals is not central to our problem. In other cases, it would perhaps be better to go over a great many men only twice each. The work might conveniently be progressive, i.e., some subjects might appear earlier than others. The only thing of importance would be that in both cases all should reappear after some predetermined interval, such as that of our 3 months. The subject of length of the period is discussed further at the end of Appendix B.

TABLE VIII. INCIDENCE OF VARIOUS RHEUMATIC MANIFESTATIONS AMONG 274 PEOPLE AT A FIRST EXAMINATION AND PERIODICALLY ONCE A QUARTER, 1958

	JAN.	FEB.	MARCH	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	MEAN
Observed Swelling													
1st exam.	8	11	16	16	21	17	11	16	13	14	11	10	13.667
2nd exam.	11	14	9	5	7	5	9	3	3				7.333
3rd exam.	5	5	4	8	3	3							4.667
4th exam.	8	2	3										4.333
Pain on Motion or Tenderness													
1st exam.	72	63	63	62	62	54	52	61	64	64	63	70	62.500
2nd exam.	19	22	20	14	25	28	24	22	30				22.667
3rd exam.	7	19	18	19	16	22							16.833
4th exam.	18	13	14										15.000
Morning Stiffness													
1st exam.	44	43	60	55	57	56	63	72	75	71	71	68	61.250
2nd exam.	23	26	12	21	33	29	24	22	14				22.667
3rd exam.	16	27	20	18	16	11							18.000
4th exam.	17	15	9										13.667
Probable Rheumatoid Arthritis													
1st exam.	6	9	13	14	13	13	11	15	13	12	10	9	11.500
2nd exam.	10	9	7	5	8	6	6	2	2				6.111
3rd exam.	5	5	5	5	2	2							4.000
4th exam.	5	1	2										2.667

APPENDIX B

On the Period Desirable Between Successive Examinations

There is a serious question of what should be the length of the period between the two examinations. The theoretical problem is that the probability of finding men in episode on re-examination must depend to some extent on the interval since the previous examination. Consider the problem in a simple form. Suppose that one were dealing with a large number of men who spend one-tenth of their time in episode. Then approximately one-tenth should be so at any first examination. Suppose now that the remaining ninth-tenths were subjected to re-examination an hour later. Then, obviously, practically no increment would be made. If, on the other hand, the second examination were deferred a month, some new cases would probably be found. The relative situation, if the second examination had been deferred for 2 months, is hard to judge in a theoretical way. Exact statements as to the effect of length of period between examinations could be made only from very elaborate plotting of the frequency distributions of the duration of episodes and interepisodes. Plainly, however, if there were any appreciable element of randomness of occurrence of episode, then a second examination after an infinite period should show about one-tenth of the nine-tenths of the men in episode. Then, the fundamental theory, Appendix C, will presumably break down if the period is very short, but it will be satisfactory if the period is very long and the subjects remain in an unchanged condition during that period. This is to say that it is necessary that the probability of a man's being in episode at the second examination is substantially the same as at the first examination. The question now becomes that of how short, in a practical way, is a very long period.

By way of empirical illumination at this point, consider evidence as in Table IX on the mean number of new cases per examination after alternative intervals of 1 month through 6 months. It can be seen that the result at second and third examination generally increases a little as the period goes up to 3 months, but then increases little more. It seems that a period of about 3 months begins to satisfy the mathematical condition of behaving as an infinite period. It will be noted that observed swelling and probable rheumatoid arthritis best meet the condition at 3 months, and pain on motion, tenderness, and morning stiffness least. Regardless of theory, in the present study we could not go beyond 3 months because it was the longest period that still provided the results of 4 examinations, as required by our theory.

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TABLE IX. NEW CASES OF VARIOUS EPISODES WITH VARIOUS INTERVALS BETWEEN EXAMINATION

	EVERY MONTH	EVERY 2 MONTHS	EVERY 3 MONTHS	EVERY 4 MONTHS	EVERY 5 MONTHS
Observed Swelling					
1st exam.	13.7	13.7	13.7	13.7	13.7
2nd exam.	5.5	6.8	7.3	7.9	6.4
3rd exam.	4.8	5.5	4.7	4.2	3.5
4th exam.	4.2	3.5	4.3		
5th exam.	3.5	2.8			
6th exam.	2.1	1.5			
Pain on Motion or Tenderness					
1st exam.	62.5	62.5	62.5	62.5	62.5
2nd exam.	19.4	21.6	22.7	23.9	24.6
3rd exam.	13.7	15.6	16.8	21.2	22.0
4th exam.	10.8	13.8	15.0		
5th exam.	10.0	14.2			
6th exam.	9.1	11.0			
Morning Stiffness					
1st exam.	61.2	61.2	61.2	61.2	61.2
2nd exam.	16.9	20.7	22.7	26.0	28.1
3rd exam.	11.6	14.5	18.0	19.5	21.0
4th exam.	8.8	12.5	13.7		
5th exam.	8.1	10.0			
6th exam.	7.1	9.0			
Probable Rheumatoid Arthritis					
1st exam.	11.5	11.5	11.5	11.5	11.5
2nd exam.	4.5	5.5	6.1	6.5	6.3
3rd exam.	3.8	4.4	4.0	4.5	3.5
4th exam.	3.1	3.5	2.7		
5th exam.	2.6	2.8			
6th exam.	2.0	1.0			

The period of 3 months may be reasonably satisfactory for stability of p, but we do not necessarily recommend it for any work that may be suggested by the present communication. For one thing, the 3 months' period may be unsatisfactory because of the seasonal effects. These are probably fairly well controlled in the present material by the arithmetic device of Table VIII in Appendix A. If we follow up the ideas that have emerged from the present study, we would probably try for preliminary examination at a uniform examination rate spread over one year. The second examination would perhaps be made for each man one year after the initial examination. Further examinations might help to check the suitability of the Pearson Type I curve.

APPENDIX C

Statistical Procedure, Derivation, and Justification

The statistical procedure of fitting a Type I distribution follows Elderton's[6] method. The steps of this method are:

I. Finding the data: E_1, the number of cases out of N possible men at the first examination, and E_2, the number of further cases at a second examination.

II. Finding the constants:

$$\left.\begin{aligned} m_1 &= \frac{N(E_1 - E_2) - E_1(E_1 + E_2)}{E_1^2 - N(E_1 - E_2)} \\ m_2 &= \frac{N(E_1 - 2E_2) - E_1(E_1 - E_2)}{E_1^2 - N(E_1 - E_2)} \end{aligned}\right\} \quad (1)$$

$$\left.\begin{aligned} A_1 &= E_1/N \\ A_2 &= (N - E_1)/N \end{aligned}\right\} \tag{2}$$

$$y_e = \frac{(m_1+1)^{m_1}\,(m_2+1)^{m_2}}{(m_1+m_2+2)^{m_1+m_2}} \cdot \frac{\Gamma\,(m_1+m_2+2)}{\Gamma\,(m_1+1)\;\Gamma\,(m_2+1)} \tag{3}$$

III. Writing the function:

$$y = y_e\left(1+\frac{x}{A_1}\right)^{m_1}\left(1-\frac{x}{A_2}\right)^{m_2} \tag{4}$$

when x has origin at the value A_1. This is a Pearson Type I function.[8] If anyone should have difficulty in recognizing Equations (1) and (2) from Elderton, the clues are that the first moment about origin of the required function is

$$\mu'_1 = E_1/N \tag{5}$$

the second moment about origin is

$$\mu'_2 = (E_1 - E_2)/N \tag{6}$$

Further, for our special case, where $x = p\text{-}A_1$, and p ranges from 0 to 1, his

$$b = A_1 + A_2 = 1 \tag{7}$$

In our discussion we regard y as f (p), the frequency distribution of individuals by fraction of time spent in episode of some kind.

The derivation and empirical justification for the above procedure starts by recognizing that the problem is to find a function of frequency of men against fraction of time in episode (of some kind), like Fig. 1, from evidence on E_1, E_2, E_3, etc., as at the top of Table X. It should be clearly understood that we cannot get the required function directly. We can, however, deduce certain important properties of these required functions, to wit, their moments. Given the moments, we can say much about their character and even resynthesize them. We may add that such studies of functions by their moments were widely employed during the statistical era dominated by the celebrated Karl Pearson, although the techniques have fallen into some disuse now.

TABLE X. MEAN NUMBER OF CASES AT FIRST EXAMINATION AND MEAN INCREMENT WITH RE-EXAMINATION EACH QUARTER TOGETHER WITH MOMENTS, BETA VALUES, AND GENERAL CHARACTER FUNCTIONS FOR VARIOUS OBSERVATIONS (N = 274)

	SYNTHETIC SWELLING	OBSERVED SWELLING	PAIN OR TENDERNESS	MORNING STIFFNESS	PROBABLE RHEUMATOID ARTHRITIS
Mean, 1st exam. E_1	18.8	13.6667	62.5000	61.2500	11.5000
Mean increment, 2d exam. E_2	7.8	7.3333	22.6667	22.6667	6.1111
Mean increment, 3d exam. E_3	5.3	4.6667	16.8333	18.0000	4.0000
Mean increment, 4th exam. E_4	4.0	4.3333	15.0000	13.6667	2.6667
μ_1'	0.068,613	0.049,878	0.228,102	0.223,540	0.041,971
μ_2'	0.040,146	0.023,114	0.145,377	0.140,815	0.019,668
μ_3'	0.031,022	0.013,382	0.124,088	0.123,784	0.011,963
μ_4'	0.026,642	0.004,866	0.109,489	0.122,567	0.009,124
β_1	12.31	11.79	2.87	3.56	16.17
β_2	15.28	5.93	3.85	5.65	22.81
Distribution type	I	near I*	I	I	I

*Imaginary in that $4\beta_2 < 3\beta_1$ and this cannot occur when the moments are calculated directly from a distribution. In the present case the fourth moment seems to have fluctuated extremely low by some combination of sampling errors.

Of the N subjects, suppose a part π spend a fraction p of their time in episode of some kind. Of the πN involved $p\pi N$ will be discovered at the first examination. $(1-p)\pi N$ will be undiscovered. Let us suppose that the chance of their being added at the next examination remains p, the circumstances being appropriate. The number then added will be $p(1-p)\pi N$. The number added at the next examination will be $p(1-p)^2\pi N$. Let us now suppose that π is a function f(p) of p as in Fig. 1. From its nature

$$\int_0^1 f(p)dp = 1 \tag{8}$$

It follows that the number of new cases at each examination will be:

$$\left.\begin{aligned}
E_1 &= \int_0^1 pf(p)\,Ndp = N\mu_1' \\
E_2 &= \int_0^1 p(1-p)\,f(p)\,Ndp = N(\mu_1'-\mu_2') \\
E_3 &= \int_0^1 p(1-p)^2\,f(p)\,Ndp = N(\mu_1'-2\mu_2'+\mu_3') \\
&\vdots \\
E_s &= \int_0^1 p(1-p)^{s-1}\,f(p)\,Ndp = N\left\{\mu_1'-(s-1)\mu_2'+\frac{(s-1)(s-2)}{1.2}\mu_3'-\ldots.\pm\mu_s'\right\}
\end{aligned}\right\} \tag{9}$$

The values μ_s' are moments about $p = 0$, the origin.

From the above simple result we see that we can get estimates of moments about origin by considering the forward difference of number of new cases at each examination. Our main problem of characterizing the required distributions is solved.

To illustrate the machinery of the above discussion in a simple numerical way, let us turn to Table II which deals with the evidence of duration of episode according to the subjects. In this table we have estimates of p, the probability of finding a man in episode, and πN, the observed frequency of such men. Operation with these values produces Table XI, which produces, as an end result, values of how many new cases should be found at each examination. To do this we note, for instance, that there are 5 men who spend 0.9700 of their time in episode. Accordingly, there is an expectation of 4.90 men at the first examination. There are 2 men who spend 0.9000 of their time in episode and they yield an expectation of 1.80 men in episode. Operating thus for each group, we get a total expectation of 18.8 men at the first examination. So far as the second episode is concerned, we note that from the group of 5 men in episode (0.9700), there is an expectation of 0.15 men undiscovered at the first examination, almost all of whom will be picked up at the second examination. Of the 2 men in episode (0.9000), there is an expectation of 0.20 men undiscovered at the first examination and, hence, an expectation of 0.18 men at the second examination. Operating thus for each group, we get a total expectation of 7.8 men at the second examination. We proceed on the same principle, examination after examination. Thus, we can go from the fairly completely known situation of Table II to the results that might be encountered in periodic examinations.

In conclusion it may be noted that the sum values (or hypothetical increments) of Table XI were employed to generate moments and then a Pearson Type curve (as below) was fitted in order to get the smooth curve of Fig. 1, for stated duration of swelling. It will, of course, be realized that the necessary moments could have been obtained direct from Table II. This approach, in

TABLE XI. SYNTHESIS OF AN ARTIFICIAL ENROLLMENT FUNCTION FROM MEN'S REPORTS ON DURATION OF SWELLING

p	0.0015	0.0045	0.0105	0.0225	0.0450	0.1000	0.1800	0.2600	0.3400	0.4200	0.5000	0.6600	0.7400	0.9000	0.9700	
$F = \pi N$	109	10	9	11	10	10	5	7	3	6	2	3	1	2	5	
EXAM.	INCREMENTS EXPECTED FROM EACH CLASS AT EACH EXAMINATION															SUM
1	0.28	0.04	0.09	0.25	0.45	1.00	0.90	1.82	1.02	2.52	1.00	1.98	0.74	1.80	4.85	18.8
2	0.28	0.04	0.09	0.24	0.43	0.90	0.74	1.35	0.67	1.46	0.50	0.67	0.19	0.18	0.15	7.8
3	0.28	0.04	0.09	0.24	0.41	0.81	0.60	1.00	0.45	0.85	0.25	0.23	0.05	0.02	0.00	5.3
4	0.28	0.04	0.09	0.23	0.39	0.73	0.50	0.74	0.29	0.49	0.12	0.08	0.01	0.00		4.0
5	0.28	0.04	0.09	0.23	0.37	0.66	0.41	0.54	0.19	0.29	0.06	0.03	0.01			3.2
6	0.28	0.04	0.09	0.22	0.36	0.59	0.33	0.40	0.13	0.16	0.04	0.01	0.00			2.6
7	0.28	0.04	0.09	0.22	0.34	0.53	0.27	0.30	0.08	0.10	0.02	0.00				2.3
8	0.28	0.04	0.09	0.21	0.33	0.48	0.22	0.22	0.06	0.05	0.00					2.0
9	0.28	0.04	0.09	0.21	0.31	0.43	0.19	0.16	0.04	0.03						1.8
10	0.28	0.04	0.09	0.20	0.30	0.39	0.15	0.12	0.02	0.02						1.6
11	0.28	0.04	0.09	0.20	0.28	0.35	0.12	0.09	0.02	0.01						1.5
12	0.28	0.04	0.08	0.19	0.27	0.31	0.10	0.07	0.01	0.01						1.4
etc.																

spite of its directness, was not made because it would have entailed more theory in the main body of the paper, and this would have hindered rather than helped our purposes.

Let us work now from the end result of the foregoing synthesis, as we do with most of our data. Consider the result for the first 4 periods, which gives 4 moments and all that can be needed. We have the following results by forward difference:

Added	Δ_1	Δ_2	Δ_3
$E_1 = 18.8$			
$E_2 = 7.8$	-11.0		
$E_3 = 5.3$	-2.5	$+8.5$	
$E_4 = 4.0$	-1.3	$+1.2$	-7.3

The leading members of each column when allowance is made for sign and for the fact that $N = 274$ give the result:

$$\left.\begin{aligned} \mu_1' &= 18.8/274 &&= +.068{,}613 \\ \mu_2' &= -(-11.0)/274 &&= +.040{,}146 \\ \mu_3' &= 8.5/274 &&= +.031{,}022 \\ \mu_4' &= -(-7.3)/274 &&= +.026{,}642 \end{aligned}\right\} \quad (10)$$

Calculation of centered moments μ_s from moments μ_s' about origin and then:

$$\left.\begin{aligned} \beta_1 &= \mu_3^2/\mu_2^3 = +12.31 \\ \beta_2 &= \mu_4/\mu_2^2 = +15.28 \end{aligned}\right\} \quad (11)$$

shows that our distribution is a Pearson[8] Type I of U-form approaching J. That is to say, it is as it should be of finite extent; we want it to run from $p = 0$ to $p = 1.0$. It has its lowest point somewhere within this range. It is very high on the left, but not very high on the right. All of this describes Fig. 1 fairly well.

The only statistical consideration now remaining is that of actually fitting or synthesizing the appropriate Type I curve. This was done by recognizing that the distribution is bounded at $p = 0$ and $p = 1$, so that only the first two moments are needed for the fitting. In doing this we simply followed Elderton,[6] replacing μ_1' and μ_2' with E_1 and E_2 from Equation (10) to produce Equations (1), (2), and (3). The resulting smooth curve is shown in Fig. 1.

Table X shows mean initial enrollment and increments with examination every 3 months taken from Table VIII; it shows the resulting moments, also the β values necessary to discover the type of Pearson[8] curve. These results are gratifying in that all distributions are essentially Type I, which has finite range, as before. This experimental fact fits admirably with our necessity of their having finite ranges from 0.0 to 1.0. In the one case which is imaginary, we may assume that this state of affairs is due to sampling error in the higher moments and that Type I distribution is indicated as in Fig. 2.

As a practical detail, it may be of interest to note the method by which the integration of the functions shown in Fig. 2 was done so that we could write Tables III and VI. It will, of course, be realized that quadrature is dangerous for a Type I function. It seems best to follow Elderton[6] and integrate over the lower range of his x (a transform of our p) in Equation (4) by transforming to $x' = x + A_1$ (our p) and writing the function as a power series. Then the upper part of the range with $x'' = x - A_2$ (the complement of our p) should be handled similarly. For the functions involved in Table VI, neither transformation worked over the entire range, $p = 0.0$ to 1.0, but integrals were obtained for a number of steps from each end of the range and the two sets overlapped handily.

The argument on the method of anticipating new cases in examinations after the second from the number of fresh cases in each of the first and second examinations is based on the fact[6] that

$$\mu_s' = \frac{m_1 + s}{m_1 + m_2 + s + 1}\,\mu_{s-1}' . \quad (12)$$

It is then simply a matter of employing μ_1' and μ_2', empirical, as a basis on which to operate backward the differencing technique previously discussed in the present section. The results to be anticipated for the third through the fifth examinations, $\hat{E}_3$ through $\hat{E}_5$, are explicit, on the basis of the known results, E_1 for the first and E_2 for the second examination.

$$\left.\begin{aligned}
\hat{E}_3 &= -E_1 + 2E_2 + \frac{m_1 + 3}{m_1 + m_2 + 4}(E_1 - E_2) \\
\hat{E}_4 &= E_1 - 3E_2 + 3\hat{E}_3 - \frac{m_1 + 4}{m_1 + m_2 + 5}(E_1 - 2E_2 + \hat{E}_3) \\
\hat{E}_5 &= -E_1 + 4E_2 - 6\hat{E}_3 + 4\hat{E}_4 + \frac{m_1 + 5}{m_1 + m_2 + 6}(E_1 - 3E_2 + 3\hat{E}_3 - \hat{E}_4)
\end{aligned}\right\} \quad (13)$$

The calculations of Equation (13) are based on empirical E_1 and E_2 together with the previously found values of m_1 and m_2, all from Table V. It is, of course, possible to go on to $\hat{E}_6$, $\hat{E}_7$, etc., but that seems injudicious.

Along the lines of Equation (13) and Table VII, it would be possible to calculate a long series of values $\hat{E}_3$, $\hat{E}_4$, $\hat{E}_5$, $\hat{E}_6$, etc., and perhaps to anticipate the total number, i.e., the sum, of cases of any given phenomenon that would be reached by a given examination. Such extrapolation from two examinations would, of course, be folly. It would not be appropriate to ask what would be the total number of cases with an infinite series of examinations, for that would be simply N, the total number of men. This result would arise from the form of f(p) as in Equation (4).

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EPIDEMIOLOGY OF ISCHEMIC HEART DISEASE AMONG WHITE MALES

I. Relationship Between Coronary Atherosclerosis and Cancer of Various Sites

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CORONARY artery disease and cancer are among the leading causes of death in the United States. Deaths from these two diseases have steadily increased in this country during the last four decades. According to some investigators, we are now witnessing "epidemics" of these presumably noninfectious diseases. A recent editorial in the *Lancet* stated: "Though some of the evidence is conflicting and insecure, it is clear that atherosclerosis and malignant disease are related in some peculiar way. It may well be that a better understanding of this relationship will lead to big advances in our knowledge of both types of disease."[1] The purpose of this study is to examine the relationship between coronary artery disease and cancer with the use of epidemiologic techniques in a necropsy population.

There have been many studies which suggest a relationship between coronary artery disease and cancer and between atherosclerosis and cancer. These studies have used both indirect and direct evidence. The age-specific death rates in the United States, England, and Western Europe from lung cancer and coronary heart disease have increased, whereas the rates for most other causes of death have declined. This indirect evidence suggests that there may be some common factors in these diseases to account for the increased death rates. Tobacco smoking has been incriminated as one of the environmental factors associated with both lung cancer and coronary artery disease. The population studies of Doll and Hill[2,3] in England and of Hammond and Horn[4,5] in the United States showed that smokers, particularly cigarette smokers, had higher mortality rates from lung cancer and coronary artery disease than nonsmokers. Retrospective case studies substantiate the association between smoking and lung cancer.[6-8] Several investigators[9,10] have reported more smokers among patients with coronary artery disease than among control groups of patients without coronary artery disease.

This paper is based on a study of the epidemiology of ischemic heart disease in partial fulfillment of the requirements for the degree of Doctor of Public Health from Yale University School of Medicine, New Haven, Conn.

Physicians have observed that occasional patients with coronary disease develop lung cancer, while others have noted that some lung cancer patients die from coronary artery disease. Are there common factors provoking these diseases or is this phenomenon merely competing causes of death in older individuals?

Other more direct evidence would seem to link together cancer and atherosclerosis. Necropsy studies point to both positive and negative associations between the two diseases. Sjövall and Wihman[11] found less atherosclerosis among cancer patients than among noncancer patients studied by them in Sweden. Wilens[12] reported that coronary atherosclerosis was less severe among patients who died from wasting diseases, including cancer, and among those who were underweight at the time of death. He suggested that there might be resorption of lipoid material from atherosclerotic deposits in these disease states. Wanscher and co-workers[13] also found less pronounced atherosclerotic lesions among cancer patients than among noncancer patients in the 1,835 autopsies they reviewed. They felt that cancer inhibited the development of atherosclerosis in some way. Lober,[14] in a study of 536 hearts, including 121 hearts of cancer victims, found that patients dying with malignant neoplasms had less severe coronary disease than did those of the same age dying from other causes. Elkeles[15] made a roentgenologic survey of calcified aortic atherosclerosis among 416 cancer patients and 700 patients without cancer. He found that the prevalence of aortic atherosclerosis was lower in patients with gastric, breast, and prostate cancer than in the control group. However, the prevalence of atherosclerosis among lung cancer patients did not differ significantly from that of the control group. Creed and his associates[16] from a study of 1,223 consecutive autopsies found that lung cancer patients had significantly more severe aortic atherosclerosis than the control group. In the same study, patients with leukemia and malignant lymphomas had significantly less aortic atherosclerosis than the control group. Therefore, previous studies of the relationship between cancer and coronary artery disease and cancer and atherosclerosis present conflicting results.

MATERIALS AND METHODS

Necropsy records, rather than clinical case reports or death certificates, were selected for this study because it was felt that macroscopic, anatomic diagnoses with histologic confirmation were more accurate than "clinical impressions." This would seem especially true where one was interested in studying cancer. Similarly, the presence and severity of coronary artery disease, in many instances, cannot be ascertained from clinical histories, physical examinations, or electrocardiographic tracings.

The data used for this study were obtained from the necropsy records of the Grace-New Haven Community Hospital, New Haven, Connecticut, which is associated with the Department of Pathology of the Yale University Medical School. This study was limited to white males 40 or more years of age, because lung cancer and coronary artery disease are most likely to occur in this group of patients. From 1935 through 1955 (a 21 year period) 2,909 autopsies were performed on white males 40 or more years of age. However, only 2,731 of the records

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among white males had the coronary arteries described in sufficient detail to be used for this study. Approximately 6 per cent (178) of the protocols were eliminated because of incompleteness.

Disease Groups.—White males 40 or more years of age were divided into the following disease groups: (1) those with cancer of various sites; (2) those dying from accidental causes; (3) those with diabetes mellitus; (4) those with ischemic heart disease; and (5) those dying from all other causes not listed in the previous categories.

Patients in the lung cancer group were limited to those who had the epidermoid and anaplastic histologic types of lung cancer, since Wynder[17] has shown that most of the increase in lung cancer cases has been limited to these histologic types, with little rise in the adenocarcinoma type. The histologic types of pulmonary neoplasms excluded were: bronchiolar or alveolar cell carcinoma, bronchial adenoma, sarcoma of the lung, mixed tumors or carcinosarcomas, neoplasms of the reticuloendothelial system involving the lungs, and metastatic tumors of the lung. Records in which the primary site of the malignant growth could not be determined were not used. If more than one primary malignant neoplasm was present in the same individual, the record was discarded. Also, any cancer patient with concomitant diabetes mellitus was excluded.

The coronary arteries of patients with cancer of various sites were studied. As in the case of lung cancer, all sarcomas, benign neoplasms, metastatic tumors, and tumors of the reticuloendothelial system were excluded in classifying carcinomas of a given site. Only primary carcinomas of the specific organ or organ system were utilized. Leukemia and sarcoma were considered as separate categories. The same criteria for "primary carcinomas" used for lung cancers were used for various other sites of cancer. The coronary arteries of patients with malignant neoplasms of the following sites were studied in detail: brain cancer; cancer of the esophagus; cancer of the stomach; cancer of the lung; cancer of the intestines and colon; cancer of the liver, pancreas, gall bladder, and bile ducts; genitourinary cancer (excluding prostate); cancer of the prostate gland; leukemia and lymphomas; and sarcomas (all sites).

Patients who died from accidental causes and who came to necropsy were used as a control group. Ideally, the control group should be representative of the general population. The question arose: What group or groups of cases in an autopsy population would be most representative of coronary artery disease in the general population? Persons who come to autopsy as a consequence of accidental deaths should constitute a suitable control group, since they are not subjected to necropsy for a specific illness. Accident victims usually have little forewarning of death. Thus, the events which produce death would have little "known" selectivity in so far as the condition of the victims' coronary arteries is concerned. To phrase it another way, the condition of these persons' coronary arteries should have little influence on their dying or their being admitted to the autopsy population. Most of the accident victims died in automobile collisions, and only one person in this study was a driver—the others were passengers.

An additional disease category, diabetes mellitus, was included for study, in the hope that this group might prove helpful in testing the reliability of the

other data. Clinical studies of living patients, autopsy investigations, death certificate analyses, life insurance experience, and community surveys have shown that diabetic persons succumb from coronary artery disease more frequently than the nondiabetic.[18-20] Thus, the diabetic group should provide a point of reference for comparison with the degree of coronary atherosclerosis found in the various other disease groups. The records of patients with diabetes mellitus listed as a diagnosis were collected in this group. Records of patients with diabetes mellitus and coexisting cancer were excluded from both the cancer and the diabetic groups.

The ischemic heart disease group included any person autopsied in whom one or more of the following conditions was listed as a finding at death: coronary thrombosis, coronary occlusion, coronary occlusion due to atherosclerosis, myocardial infarction, angina pectoris, and coronary insufficiency. These conditions did not have to be listed as the primary cause of death to be included in the ischemic heart disease category. If any of the above conditions occurred in a diabetic patient, they were not included in the ischemic heart disease group, but, rather, in the diabetic group. Any patient with ischemic heart disease who died with cancer or from accidental causes was placed in the appropriate cancer group or accident group.

Patients who could not be placed in one of the cancer groups, the accident group, the diabetes mellitus group, or the ischemic heart disease group were assigned to a category, "all other diseases."

Certain diseases are associated with the development of coronary artery disease. They include diabetes mellitus, familial xanthomatosis, essential hyperlipemia, myxedema, syphilitic coronary narrowing, thromboangiitis obliterans, polycythemia, congenital defects, polyarteritis nodosa, infectious diseases producing coronary arteritis, and aneurysms. As mentioned previously, patients with diabetes mellitus were treated as a separate disease group. Inspection of the various disease groups showed that the above conditions were not a major source of bias.

Matching Records.—Numerous studies have shown that coronary atherosclerosis is more prevalent among males than among females, among whites than among non-whites, and among elderly persons than among young persons. Therefore, this study was limited to white males. Age was adjusted for by a technique of "balancing" described by Cochran.[21] For age, the records were balanced so that the mean age for the various groups (lung cancer, gastrointestinal cancer, accidents, diabetes, etc.) was equal. In no instance was a record used in this balancing process if the difference in the ages of subjects in the various groups was greater than 5 years. Another covariable taken into account was the year that death occurred. This covariable seemed important, since there is indirect evidence that coronary artery disease is on the increase. Year of death was adjusted for by matching the records in the various disease groups by 5 year periods (for example, 1935-1939, 1940-1944, 1945-1949, etc.). Hypertension was not considered an important source of bias in comparing cancer patients with accident victims, since 19 per cent of the accident victims and 22 per cent of the combined cancer patients had hypertension. Also, there was no great variation

in the percentage of patients with hypertension among the various specific cancer groups. While the percentage of accident victims with hypertension may have been understated, this was not thought to be a major source of error. Obesity is another covariable which has been implicated in coronary atherosclerosis.[12] The Metropolitan Life Insurance Company data on the weight and height of white males over the age of 25 were used to calculate the percentage of patients who were 15 per cent or more underweight and those who were 15 per cent or more overweight. It must be recognized, however, that the weight of a patient at time of death may not be representative of his weight throughout most of life. This attempt to adjust for body weight is crude, but it is the best that can be done with autopsy data.

Classification of Coronary Disease.—A random sample of 200 autopsy reports was examined to devise a classification of coronary artery disease which would fit the available data rather than trying to make the data conform to a prearranged classification. Although these necropsies were performed by many different individuals during the period from 1935 through 1955, the heart descriptions remained surprisingly complete and uniform. The heart was examined in a systematic fashion and there was a complete record of the normal and pathologic findings of the epicardium, myocardium, endocardium, heart chambers, cardiac valves, great vessels, and coronary arteries. The heart was described in greater detail than any other organ in these necropsies. What is more important, the descriptions of normal hearts were as complete as those of diseased hearts, and the hearts of patients who died from noncardiac causes were described as thoroughly as those of patients who died from heart disease. Also, the pathologists often stated negative findings, for example, "The coronary arteries were smooth, were not obstructed, and there was no calcification or atheromatous plaque formation present."

Many previous studies have failed to take into account that partial or complete coronary blockage may result from atherosclerosis or clot (thrombosis or embolism) or a combination of the two. The grading of coronary artery blockage in this study was based primarily on the macroscopic description of the arteries. Microscopic descriptions of the arteries were used, in some instances, to confirm the gross observations. Coronary artery blockage was classified as follows:

Grade of coronary blockage due to atherosclerosis:

0. Cases without macroscopic evidence of atherosclerosis or thickening and scarring of the vessel wall.

I. Cases showing atherosclerotic changes as indicated by plaques, thickening of the vessel wall, and calcification in which narrowing of the vessel lumen ranged from 1 to 49 per cent.

II. Cases showing atherosclerotic changes which produced narrowing of the vessel lumen from 50 to 89 per cent.

III. Cases with atherosclerotic changes producing narrowing of the vessel lumen from 90 to 99 per cent.

IV. Cases with atherosclerotic lesions which completely obliterated the vessel lumen—100 per cent blockage.

Grade of coronary blockage due to clot:

A. Clot absent.

B. Clot present.

Usually when no macroscopic atherosclerosis was present it was stated, "No atherosclerosis was seen." However, in some instances, the prosector merely stated, "No coronary artery pathology was evident." These records were classified as Grade 0. The cases of minimal atherosclerosis were usually described as, "Athermatous plaques are present but they do not encroach on the vessel lumen," or "There are patches of atheromatous deposits scattered throughout the coronary arteries but they do not obstruct the vessel lumen to any considerable degree." These cases were classified in Grade I, 1 to 49 per cent blockage. For Grade II and III blockage the pathologists in about one half of the cases estimated the amount of blockage as 60 per cent, 80 per cent, 95 per cent, etc. Also included in Grade III were cases in which the lumen was described as, "pin point in diameter" or "not completely obstructed but the lumen was so narrow as not to permit the passage of blood." The cases in Grade IV were straightforwardly described as "completely blocked" or "completely occluded" or "totally obstructed" by atheromatous deposits. Actually, very little difficulty was experienced in assigning a case to the appropriate "grade of blockage." Two observers, other than the author, were given a random sample of these necropsy heart descriptions and were asked independently to classify the coronary arteries into the various grades. There was 93 per cent agreement among the observers (including the author) concerning grades to which the cases should be assigned.

This classification refers to the most severely diseased coronary artery or one of its major branches as described in the autopsy protocol. To familiarize the reader with this classification, several examples are given. The classification II-A denotes atherosclerosis which narrows the vessel lumen from 50 to 89 per cent with no clot present, whereas II-B indicates atherosclerosis blocking the lumen 50 to 89 per cent with a clot present. The clot may partially or completely block the remainder of the lumen. It was not unusual to find more than one artery or major branch described as containing significant blockage. For example, if the left main coronary artery had I-A, the right coronary had II-A, and the left anterior branch had III-A, then III-A was selected as representing the most severely blocked arterial segment. When two different arteries exhibited the same amount of blockage but by different processes (for example, III-B and IV-A), the final classification was determined by a process of random numbers. There were 23 instances in which this phenomenon occurred.

RESULTS

The relationship between coronary atherosclerosis and cancer was examined by matching the records of cancer patients with those of accident victims. Each cancer patient's record was compared with that of an accident victim of the same age, sex, and race who had died during the same 5 year period. Other variables adjusted for were hypertension, body weight, and diseases known to influence the development of coronary atherosclerosis. Accident victims' records were

matched with the records of patients who had cancer of the following primary sites: lung, 132 records; laryngeal and upper respiratory tract, 65 records; genitourinary tract (excluding prostate), 62; esophagus, 41; stomach, 77; intestines, 94; leukemia and lymphoma, 69; liver, pancreas, gall bladder, and bile ducts, 48; prostate, 78; sarcoma, 37; and brain, 67. As seen in Table I, there was no significant difference in the amount of coronary blockage resulting from atherosclerosis among any of the cancer groups when they were compared with the control group of accident victims. The chi-square test for significance was used in these analyses. Table I was retested by combining Grade II and Grade III blockage into one group. Again the results were not statistically significant, even in the case of cancer of the prostate where a p value of <0.10 but > 0.05 was obtained.

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TABLE I. CORONARY ARTERY BLOCKAGE DUE TO ATHEROSCLEROSIS AMONG PATIENTS DYING WITH CANCER OF VARIOUS SITES AND AMONG THOSE DYING FROM ACCIDENTAL CAUSES

DISEASE	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE					TOTAL	TEST FOR SIGNIFICANCE—p
	0	I	II	III	IV	NO.	
Lung cancer	38	67	13	10	4	132	< 0.70 but > 0.50
Accidents	32	66	21	10	3	132	
Laryngeal and upper respiratory cancer	19	28	14	4	0	65	< 0.70 but > 0.50
Accidents	17	30	9	8	1	65	
Genitourinary cancer (excluding prostate)	11	29	12	7	3	62	< 0.98 but > 0.95
Accidents	13	31	10	6	2	62	
Esophageal cancer	11	19	8	1	2	41	< 0.99
Accidents	10	18	7	4	2	41	
Stomach cancer	22	33	13	8	1	77	< 0.80 but > 0.70
Accidents	23	38	9	5	2	77	
Intestinal cancer	22	44	14	11	3	94	< 0.80 but > 0.70
Accidents	20	41	21	10	2	94	
Leukemia and lymphoma	23	31	10	5	0	69	< 0.70 but > 0.50
Accidents	22	35	6	5	1	69	
Liver, pancreas, and gall bladder cancer	11	23	10	3	1	48	< 0.95 but > 0.90
Accidents	12	24	7	3	2	48	
Prostate cancer	9	28	17	17	7	78	< 0.20 but > 0.10
Accidents	14	37	15	10	2	78	
Sarcoma, all sites	12	19	3	3	0	37	< 0.80 but > 0.70
Accidents	18	15	2	2	0	37	
Brain cancer	28	29	5	3	2	67	< 0.70 but > 0.50
Accidents	22	31	7	6	1	67	

Since the records of the individual sites of cancer showed no essential difference from the accident records in so far as atherosclerotic blockage of the coronary arteries was concerned, all cancer records were pooled together and compared with all accident records. As one might have presupposed, Table II shows that the combined cancer records and the combined accident records were not significantly different for atherosclerotic blockage. The reason for examining the records in this way becomes apparent later.

TABLE II. GRADES OF CORONARY ARTERY ATHEROSCLEROTIC BLOCKAGE AMONG CANCER RECORDS, ALL SITES, AND AMONG POOLED ACCIDENT RECORDS IN AN AUTOPSY POPULATION

AGE GROUP (YEARS)	DISEASE GROUP	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE										TOTAL	
		0		I		II		III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	Cancer	51	59	30	34	4	5	2	2	0	0	87	100
	Accidents	26	46	24	43	4	7	1	2	1	2	56	100
50–59	Cancer	75	36	99	48	19	9	14	7	1	<1	208	100
	Accidents	15	29	24	47	7	14	4	8	1	2	51	100
60–69	Cancer	44	18	130	54	31	13	26	11	11	4	242	100
	Accidents	6	15	21	54	8	20	3	8	1	3	39	100
70+	Cancer	27	12	91	40	64	28	33	15	12	5	227	100
	Accidents	5	12	21	49	11	25	5	12	1	2	43	100
Total	Cancer	197	26	350	46	118	15	75	10	24	3	764	100
	Accidents	52	27	90	48	30	16	13	7	4	2	189	100

Results: No significant difference between cancer and accident cases.

It seemed advisable to look at the cancer records in the conventional way that autopsy data are examined, namely, to compare the pooled cancer records with "all other records" in the total autopsy population. "All other records" in this analysis refers to the record of every patient who died of some disease other than cancer. This includes patients dying of diabetes mellitus, ischemic heart disease, accidents, and all other diseases except cancer. Adjustments were made for age, sex, and race. Table III shows that the pooled cancer records showed less advanced blockage from atherosclerosis than "all other records" in the autopsy population. The chi-square test for these data provided a significant difference for the total and every age group except the 70-and-over group. Thus, entirely different results were obtained when cancer records were compared with accident records (Table II) than when cancer records were compared with "all other records" in the autopsy population (Table III). These conflicting results will be discussed later.

Since no significant difference in the severity of coronary atherosclerosis was found among cancer patients and accident victims, it seemed important to compare the coronary arteries of these patients with the coronary arteries of

TABLE III. GRADES OF CORONARY ARTERY ATHEROSCLEROTIC BLOCKAGE AMONG CANCER PATIENTS, ALL SITES, AND AMONG ALL OTHER (NONCANCER) PATIENTS IN AN AUTOPSY POPULATION

AGE GROUP (YEARS)	DISEASE GROUP	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE										TOTAL	
		0		I		II		III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	Cancer	51	59	30	34	4	5	2	2	0	0	87	100
	All others	210	44	171	36	40	9	43	9	11	2	475	100
50–59	Cancer	75	36	99	48	19	9	14	7	1	<1	208	100
	All others	137	28	184	37	79	16	68	14	25	5	493	100
60–69	Cancer	44	18	130	54	31	13	26	11	11	4	242	100
	All others	90	17	184	35	104	20	112	21	39	7	529	100
70+	Cancer	27	12	91	40	64	28	33	15	12	5	227	100
	All others	51	11	191	41	118	25	94	20	16	3	470	100
Total	Cancer	197	26	350	46	118	15	75	10	24	3	764	100
	All others	488	25	730	37	341	17	317	16	91	5	1,967	100

Results: (When Grades II and III are combined into one group)	AGE GROUP	p
	40-49	< 0.02 but > 0.01
	50-59	< 0.001
	60-69	< 0.001
	70+	< 0.70 but > 0.50
	Total	< 0.001

patients in whom one would expect to find an excessive amount of severe atheromatous blockage. There was the possibility that cancer and accident patients had excessive amounts of atherosclerotic blockage. Patients with diabetes mellitus are known to have more severe coronary atherosclerosis and more ischemic heart disease than the general, nondiabetic population. Hence, a comparison of coronary atherosclerotic blockage was made among patients with lung cancer, gastrointestinal cancer, accidents, and diabetes mellitus. A total of 380 matched records was used for this purpose—95 in each disease category. From Table IV it is obvious that fewer diabetic patients escaped having coronary atherosclerosis. Eight with diabetes lacked atherosclerosis while 27 to 30 patients in each of the other disease groups lacked atherosclerosis. Also, 32 diabetic patients had Grade IV (complete) blockage while only 3 to 6 accident and cancer patients had Grade IV blockage. A chi-square value of 65.581 and a p value of < 0.001 were found, indicating a highly significant difference. This suggests that accident and cancer patients do not have an excessive amount of coronary atherosclerotic blockage.

Coronary artery clot formation (thrombosis or embolism) is important in the pathogenesis of ischemic heart disease. It is thought that clot formation most often results as a complication of atheroma. No significant difference in coronary clot formation was found when coronary arteries of patients in the 11 individual cancer groups were compared with the coronary arteries of matched accident victims. Therefore, cancer patients' records were pooled and compared with

accident victims' records for the presence or absence of coronary artery clot formation. As seen in Table V, the results of this analysis were not significant.

Coronary artery clots among the pooled cancer patients then were compared with clots among "all other records" in the autopsy population (Table VI). With the exception of the age group from 40 to 49 years, a highly significant difference was observed for each age group. This method of analysis would suggest that cancer patients have significantly fewer coronary artery clots than "all other" patients in the autopsy population.

TABLE IV. COMPARISON OF GRADES OF CORONARY ARTERY ATHEROSCLEROTIC BLOCKAGE AMONG MATCHED LUNG CANCER, GASTROINTESTINAL CANCER, DIABETES MELLITUS, AND ACCIDENT PATIENTS

DISEASE GROUP	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE					TOTAL
	0	I	II	III	IV	
Lung cancer	27	42	12	9	5	95
Gastrointestinal cancer	30	44	11	7	3	95
Accidents	27	46	11	5	6	95
Diabetes mellitus	8	38	8	9	32	95
Total	92	170	42	30	46	380

Results: $\chi^2 = 65.581$, d.f. = 12, p = < 0.001.

TABLE V. COMPARISON OF CORONARY ARTERY CLOTS AMONG CANCER PATIENTS, ALL SITES, AND ACCIDENT PATIENTS IN AN AUTOPSY POPULATION, BY AGE GROUPS

AGE GROUP (YEARS)	DISEASE GROUP	CORONARY CLOT				TOTAL	
		PRESENT		ABSENT			
		NO.	%	NO.	%	NO.	%
40–49	Cancer, all sites	1	1	86	99	87	100
	Accidents	0	0	56	100	56	100
50–59	Cancer, all sites	3	1	205	99	208	100
	Accidents	0	0	51	100	51	100
60–69	Cancer, all sites	11	5	231	95	242	100
	Accidents	3	8	36	92	39	100
70+	Cancer, all sites	10	4	217	96	227	100
	Accidents	3	7	40	93	43	100
Total	Cancer, all sites	25	3	739	97	764	100
	Accidents	6	3	183	97	189	100

Results: No significant difference between cancer and accident cases.

TABLE VI. COMPARISON OF CORONARY ARTERY CLOTS AMONG CANCER PATIENTS, ALL SITES, AND ALL OTHER (NONCANCER) PATIENTS IN AN AUTOPSY POPULATION, BY AGE GROUPS

AGE GROUP (YEARS)	DISEASE GROUP	CORONARY CLOT				TOTAL	
		PRESENT		ABSENT			
		NO.	%	NO.	%	NO.	%
40–49	Cancer	1	1	86	99	87	100
	All others	27	6	448	94	475	100
50–59	Cancer	3	1	205	99	208	100
	All others	58	12	435	88	493	100
60–69	Cancer	11	5	231	95	242	100
	All others	94	18	435	82	529	100
70+	Cancer	10	4	217	96	227	100
	All others	74	16	396	84	470	100
Total	Cancer	25	3	739	97	764	100
	All others	253	13	1,714	87	1,967	100

Results:

AGE GROUP	p
40-49	< 0.10 but > 0.05
50-59	< 0.001
60-69	< 0.001
70+	< 0.001
Total	< 0.001

Body weight was a factor which had not been taken into consideration in the matching process. Approximately 30 per cent of the cancer patients were underweight and 15 per cent were overweight at the time of death. On the other hand, 14 per cent of the accident victims were underweight and 30 per cent were overweight at the time of death. Therefore, the records of all cancer patients and accident victims in the normal range of weights at the time of death were compared. Tables VII and VIII show that no essential difference was found in the severity of coronary atherosclerotic blockage or coronary clot formation when cancer patients were compared with accident victims. This analysis seems to indicate that the previous findings in this study cannot be attributed to differences in body weight among the patients studied.

DISCUSSION

An autopsy population represents a collection of pathologic conditions which, in most instances, is not representative of the hospital population or of the general population from which they originated. Mainland[22] has presented a thought-provoking discussion of the various antemortem and postmortem factors which may influence a patient's selection to or rejection from an autopsy population. Other biostatisticians[23,24] are in accord with Mainland's ominous warning that there are many pitfalls and sources of bias in using autopsy data. These authors suggested matching the experimental group with the control group for variables

TABLE VII. GRADES OF CORONARY ATHEROSCLEROTIC BLOCKAGE AMONG PATIENTS WITH CANCER, ALL SITES, AND AMONG ACCIDENT VICTIMS, BY AGE GROUPS (ALL PATIENTS WITHIN AVERAGE RANGE OF BODY WEIGHT AT TIME OF DEATH)

AGE GROUP (YEARS)	DISEASE GROUP	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE										TOTAL	
		0		I		II		III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	Accidents	12	46	11	42	2	8	1	4	0	0	26	100
	Cancer	19	44	21	49	2	5	1	2	0	0	43	100
50–59	Accidents	6	25	9	38	6	25	2	8	1	4	24	100
	Cancer	29	32	45	49	12	13	5	5	1	1	92	100
60–69	Accidents	5	18	14	50	6	21	2	7	1	4	28	100
	Cancer	21	19	52	47	18	16	14	13	5	5	110	100
70+	Accidents	2	9	10	46	6	27	4	18	0	0	22	100
	Cancer	13	11	51	42	30	25	23	19	4	3	121	100
Total	Accidents	25	25	44	44	20	20	9	9	2	2	100	100
	Cancer	82	22	169	46	62	17	43	12	10	3	366	100

Results: No significant difference between cancer and accident cases.

TABLE VIII. CORONARY ARTERY CLOTS AMONG PATIENTS DYING WITH CANCER, ALL SITES, AND AMONG THOSE DYING FROM ACCIDENTS, BY AGE GROUPS (ALL PATIENTS WITHIN AVERAGE RANGE OF BODY WEIGHT AT TIME OF DEATH)

AGE GROUP (YEARS)	DISEASE GROUP	CORONARY CLOT				TOTAL	
		PRESENT		ABSENT			
		NO.	%	NO.	%	NO.	%
40–49	Accidents	0	0	26	100	26	100
	Cancer	0	0	43	100	43	100
50–59	Accidents	0	0	24	100	24	100
	Cancer	3	3	89	97	92	100
60–69	Accidents	2	7	26	93	28	100
	Cancer	6	5	104	95	110	100
70+	Accidents	1	5	21	95	22	100
	Cancer	9	7	112	93	121	100
Total	Accidents	3	3	97	97	100	100
	Cancer	18	5	348	95	366	100

Results: No significant difference between cancer and accident cases.

such as age, sex, race, and other conditions which are known to influence the development of the disease being studied. These suggestions were followed in the present study to help eliminate bias. It is difficult in experimental studies to

match the control and experimental groups for every variable except the one being studied. However, an effort was made in this study to adjust for some of the more important variables "known" to influence the development of coronary atherosclerosis.

Three serious limitations of the retrospective (case) method of study—incomplete records, lack of uniformity, and more detailed descriptions of interesting cases—were not encountered in this study. The autopsy heart and coronary artery descriptions for the period 1935 to 1944 were just as complete and consistent as those for the period 1945 to 1955. Only 6 per cent of the records in this study could not be used because of incompleteness. There has been a keen interest in coronary artery disease in the department during the 21 year period. Winternitz and his associates[25] gathered the material for their book, *The Biology of Arteriosclerosis*, from this autopsy population. Since that time, several members of the department have continued studying the coronary arteries. The technique for examining them and the method of recording the findings has not changed materially over the years. The coronary arteries were examined routinely in all necropsies. Observer bias in describing the coronary arteries of especially interesting cases appeared inconsequential. Perhaps this thoroughness is related to tradition in pathology, to the accessibility of the heart for study, and to the fact that pathologic changes in the heart are commonplace.

The method of classifying coronary artery pathology in this study takes into consideration only the most completely blocked artery and neglects the condition of the other coronary arteries. Clearly, then, this classification is a functional one, based on blockage of a vessel lumen. Since this was a retrospective study, it was not possible to measure quantitatively the amount of atherosclerosis in the coronary arteries. One wonders if the total amount of atherosclerosis really is as important in the pathogenesis of ischemic heart disease (angina pectoris, myocardial infarction, coronary insufficiency, etc.) as the amount of blockage produced by atherosclerosis. There may have been some overlapping of cases in the various grades of atherosclerotic blockage, but this was not felt to be a serious problem. Analyses of the data with different combinations of the grades produce essentially the same conclusions.

Berkson[26] of the Mayo Clinic has pointed out that a very serious fallacy may occur in necropsy studies under two sets of circumstances: (1) if two diseases in the same person increase the probability of his admission to the autopsy population, or (2) if persons with the diseases are not represented in the autopsy population in the same proportion that they are found in the general population. Kraus[27] pointed out that Berkson's fallacy is less likely to occur when a characteristic, such as eye color or smoking, is compared with a disease than when two or more diseases are compared with each other.

Many studies based on necropsy records compare the incidence of a disease or condition (X) in disease A with the incidence of X in all other autopsy records (all non-A records). Some pathologists falsely assume that such a comparison is less likely to be biased if they use "consecutive" autopsies. They do this without taking into account the many antemortem and postmortem selection factors. There is a real possibility that the all non-A records (control) group is biased.

An example of Berkson's fallacy was found in this autopsy study. There was no significant difference in the severity of coronary atherosclerotic blockage when cancer patients were compared with accident victims (Tables I and II). However, there was significantly less severe coronary atherosclerotic blockage among cancer patients when they were compared with all other patients (all noncancer patients) in the autopsy population (Table III). Likewise, no significant difference in coronary artery clot formation was found between cancer patients and accident victims (Table V). However, cancer patients had significantly fewer coronary artery clots when they were compared with all other patients in the autopsy population (Table VI).

Accident victims should provide a suitable control group, since the condition of their coronary arteries would not be expected to influence their admission to the autopsy population to any considerable extent. Obviously, the "all other (noncancer) diseases" group in this autopsy population is a biased one. Records of noncancer groups are heavily weighted with patients who had coronary atherosclerosis because of an unusually high proportion of patients with atherogenic conditions. For example, there were more patients who had diabetes mellitus in the autopsy population than one would expect to find in the general population. The fact that most previous studies[11-14,16] of the relationship between cancer and atherosclerosis were based on a comparison of cancer records with "all other (noncancer) records" in a necropsy population would tend to invalidate the results obtained. Most likely, the noncancer records in these studies were heavily weighted for atherosclerosis; therefore, one is not surprised that, in most instances, a negative correlation was found between cancer and atherosclerosis. The present study seems to indicate no association—either positive or negative—between cancer and coronary atherosclerosis. This example of Berkson's fallacy should caution pathologists that this fallacy is not merely a figment in the minds of biostatisticians.

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SUMMARY

1. An epidemiologic study was made of the relationship between cancer and ischemic heart disease among white males, utilizing an autopsy population. The coronary arteries of patients with cancer of 11 different sites were compared with the coronary arteries of accident victims. The records were matched for age, sex, race, year of death within a 5 year limit, and other factors known to influence the prevalence of coronary atherosclerosis. Adjustments were made also for hypertension and body weight at time of death. Next, the coronary arteries of cancer patients were compared with those of "all other (noncancer) patients" in the autopsy population.

2. There were no significant differences in the severity of coronary artery atherosclerotic blockage or coronary clot formation when cancer patients were compared with accident victims. However, cancer patients had significantly less severe coronary artery atherosclerotic blockage and fewer coronary clots when they were compared with all other (noncancer) patients in the autopsy population. These conflicting results constitute an example of Berkson's fallacy. It was reasoned that accident victims were the group in the autopsy population whose

coronary arteries should be most representative of those of the general population. On the other hand, the coronary arteries of all other (noncancer) patients in the autopsy population were heavily weighted with atherosclerotic conditions such as ischemic heart disease, diabetes mellitus, and hypertension.

3. It was concluded that there is no association—either positive or negative—between cancer and coronary artery atherosclerotic blockage or coronary artery clot formation. This finding appears to contradict recent epidemiologic and pathologic evidence which tended to link together cancer, especially lung cancer, and atherosclerosis.

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EPIDEMIOLOGY OF ISCHEMIC HEART DISEASE AMONG WHITE MALES

II. Autopsy Incidence of Ischemic Heart Disease and Autopsy Prevalence of Coronary Atherosclerosis

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HAS there been an actual increase in coronary atherosclerosis and ischemic heart disease in the United States? Some persons feel that ischemic heart disease has become an "epidemic" disease among the adult males in our population. On the other hand, Master[1] expressed the opinion that coronary heart disease is not a new disease and that it has not assumed "epidemic" proportions.

Mortality rates for arteriosclerotic heart disease, including coronary disease, have been on the increase in this country since 1900. However, death registration in the United States was incomplete before 1933. According to Woolsey and Moriyama[2] it was not until about 1926 that deaths from coronary disease began appearing with great frequency on death certificates in the United States. The popularity of certifying deaths as resulting from coronary disease followed Herrick's[3,4] reports in 1912 and 1919 calling coronary thrombosis to the attention of the American medical profession. Because of frequent changes in the classification of heart disease in the "International List of Causes of Death" and the "Manual of the Joint Causes of Death," mortality analyses are of somewhat limited value in studying the trends of ischemic heart disease. Lew[5] attributed the increased crude death rate from coronary disease to a greater proportion of persons in the older age groups, to changes in the classification of heart disease, to better diagnosis by physicians, and to increasing usage of the term "coronary artery disease" in certifying causes of death. He felt that probably less than 15 per cent of the increased death rate could be attributed to a "real" increase in mortality from coronary disease. On the other hand, Moriyama[6] found that physicians in Pennsylvania certified deaths resulting from cardiovascular-renal diseases on the basis of reasonably good or better diagnostic criteria. This finding would tend to increase one's confidence in using death certificates for epidemiologic studies of ischemic heart disease.

Other evidence to suggest a real increase in ischemic heart disease comes from clinical and pathologic studies. White[7] expressed the opinion that he was

This paper is based on a study of the epidemiology of ischemic heart disease in partial fulfillment of the requirements for the degree of Doctor of Public Health from Yale University School of Medicine, New Haven, Conn.

seeing more coronary heart disease today in his practice than he saw 20 years ago. Twenty per cent of 3,000 cardiac patients he examined in 1925 had coronary heart disease, whereas 48.5 per cent of 3,000 patients he examined in 1950 had coronary heart disease. Apparently, ischemic heart disease is being diagnosed more frequently in younger persons today. Yater and his associates[8] reported 866 cases of coronary artery disease which occurred among persons 18 to 39 years of age in the Armed Forces during World War II. More recently Enos, Holmes, and Beyer[9] found that 77.3 per cent of 300 young American soldiers killed in action in Korea had gross evidence of coronary atherosclerosis. Thomas, Blache, and Lee[10] reported an increased autopsy incidence of myocardial infarction among white persons in St. Louis, New Orleans, and Washington, D. C., in the period 1940-1954 over the period 1910-1939. Other investigators[11,12,13] have found similar increases in the incidence of coronary heart disease in various autopsy populations. Morris[13] in a study of the necropsy records at the London Hospital found an increased incidence of coronary heart disease, but a decreased prevalence of coronary atherosclerosis. This latter finding is somewhat difficult to interpret. Most of the evidence points in the same direction, namely, that coronary or ischemic heart disease is being seen more often today and that deaths from this cause have increased. In this an "apparent" or a "real" increase?

The purpose of this investigation is to study the epidemiology of ischemic heart disease among white males in a necropsy population in an effort to ascertain whether or not the autopsy incidence of ischemic heart disease has increased over the years, to determine whether the prevalence of coronary atherosclerosis has increased in a group of patients whose coronary arteries are representative of those of the general population, and to discover the factors associated with coronary atherosclerosis. Most authorities agree that the basic pathologic lesion in most cases of ischemic heart disease is coronary atherosclerosis and its complications. Therefore, a "real" increase in the incidence of ischemic heart disease should be accompanied by an increased prevalence of coronary atherosclerosis. Progress in understanding the etiology of ischemic heart disease has been retarded somewhat because most studies have been based on findings at the far extreme of the biologic gradient of the disease—clinical ischemic heart disease in the living and postmortem findings in those who died of the disease. At the present time milder forms of coronary artery atherosclerosis cannot be ascertained in the living, hence we must turn to an autopsy population for many of the answers to this problem.

MATERIALS AND METHODS

This study is based on the findings in 2,731 white males 40 or more years of age who came to necropsy at the Grace–New Haven Community Hospital, New Haven, Connecticut, during the 21 year period from 1935 through 1955.

The autopsy incidence of ischemic heart disease during four periods of time, 1935-1939, 1940-1944, 1945-1949, 1950-1955, was calculated by determining the percentage of white males who had ischemic heart disease at death among the total number of white males who were autopsied during the period. Ischemic heart

disease was defined as being present when one or more of the following conditions were listed in any autopsy record: coronary thrombosis, coronary occlusion, coronary occlusion due to atherosclerosis, myocardial infarction, angina pectoris, and coronary insufficiency. Any patient with one or more of these findings and concomitant diabetes mellitus was *not* included in the ischemic heart disease group. Therefore, for the most part, these are typical uncomplicated cases of ischemic heart disease among white males 40 or more years of age.

In the first portion of this study[14] the coronary arteries of cancer patients were compared with the coronary arteries of accident victims. No significant difference in the amount of coronary atherosclerotic blockage or coronary clot formation was found. Because of the remarkable consistency of these records after most of the major factors known to influence the development of coronary atherosclerosis were taken into account, it was felt that the combined accident and cancer records were the autopsy records most representative of the coronary arteries of the general population. If one accepts this hypothesis, then the autopsy prevalence of coronary atherosclerosis and the factors which influence its development can be studied. The definition of cancer and accident victims, the classification of coronary atherosclerotic blockage and coronary clot formation, and the technique of matching the records were presented in the first part of this study.[14]

RESULTS

The consensus among practicing physicians and pathologists is that patients with ischemic heart disease are being seen more frequently today than they were 20 years ago. Since the hearts and coronary arteries of patients in this autopsy population have been examined routinely over a 21 year period, it seemed advisable to determine whether the autopsy incidence of ischemic heart disease had increased (Table I). The incidence per 100 autopsies during the different time periods was: 12.15 for 1935-1939; 11.27 for 1940-1944; 15.13 for 1945-1949; and 18.44 for 1950-1955. The two former periods were combined to give an incidence of 11.66 for 1935-1944. This was compared with the rate of 16.98 for the two latter periods, 1945-1955. This difference in incidence was statistically significant at the $p = < 0.001$ level. Therefore, there has been a definite increase in the incidence of ischemic heart disease in this autopsy population during the past 21 years.

An increased prevalence of coronary atherosclerosis in a "control group" in the same autopsy population would tend to support the increased autopsy incidence of ischemic heart disease as being real. If one assumes that the coronary artery disease of accident and cancer victims is reasonably representative of that of the general population during the same period of time, then the prevalence of coronary atherosclerosis can be determined. The hypothesis that there has been an increase in the prevalence of coronary atherosclerosis was tested by separating the accident-cancer autopsy records into two periods of time, 1935-1944 and 1945-1955. The records in these two periods were then arranged in four groups according to age at time of death. Table II gives the autopsy prevalence

TABLE I. AUTOPSY INCIDENCE OF ISCHEMIC HEART DISEASE AMONG WHITE MALES, 40-89 YEARS OF AGE, FROM 1935 THROUGH 1955

PERIOD OF TIME	TOTAL NO. AUTOPSIES	NO. CASES DIAGNOSED AS ISCHEMIC HEART DISEASE*	RATE OF ISCHEMIC HEART DISEASE/100 AUTOPSIES
1935-1939	543	66	12.15
1940-1944	692	78	11.27
1945-1949	661	100	15.13
1950-1955	835	154	18.44
Total	2,731	398	14.57

*Excluding cases of ischemic heart disease and coexistent diabetes mellitus.

TABLE II. PREVALENCE OF CORONARY ARTERY ATHEROSCLEROTIC BLOCKAGE, BY AGE GROUPS, AMONG WHITE MALES FOR THE PERIODS 1935-1944 VERSUS 1945-1955. BASED ON FINDINGS IN CANCER PATIENTS AND ACCIDENT VICTIMS

AGE GROUP (YEARS)	PERIOD OF TIME	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE										TOTAL	
		0		I		II		III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	1935–44	53	66	24	30	2	3	1	1	0	0	80	100
	1945–55	36	42	38	44	9	11	2	2	1	1	86	100
50–59	1935–44	50	40	56	45	13	11	4	3	1	1	124	100
	1945–55	49	35	64	45	14	10	14	10	0	0	141	100
60–69	1935–44	29	27	55	50	10	9	11	10	4	4	109	100
	1945–55	25	13	99	52	35	19	21	11	10	5	190	100
70+	1935–44	20	19	58	57	14	14	8	8	2	2	102	100
	1945–55	16	8	76	38	64	32	33	17	11	5	200	100

Results: (When Grades II and III are combined into one group)	AGE GROUP	p
	40-49	< 0.01 but > 0.001
	50-59	< 0.50 but > 0.30
	60-69	< 0.02 but > 0.01
	70+	< 0.001

of coronary atherosclerosis for 1935-1944 and 1945-1955. This table clearly points out that there was a higher percentage of persons entirely free of atherosclerosis in every age group in 1935-1944 than in 1945-1955. Furthermore, when Grades II, III, and IV (50 to 100 per cent) atherosclerotic blockage were combined to indicate "advanced" atherosclerosis, an increased prevalence of "advanced" atherosclerosis was found for every age group during the latter period, 1945-1955. This alarming increase in "advanced" coronary atherosclerosis is shown in Fig. 1. The ratios of cases of "advanced" atherosclerosis in 1935-1944 compared with 1945-1955 for the same age groups were: 1 to 3.5 at ages 40-49; 1 to 1.3 at ages 50-59; 1 to 1.5 at ages 60-69; and 1 to 2.3 at ages 70 or more. Therefore, the

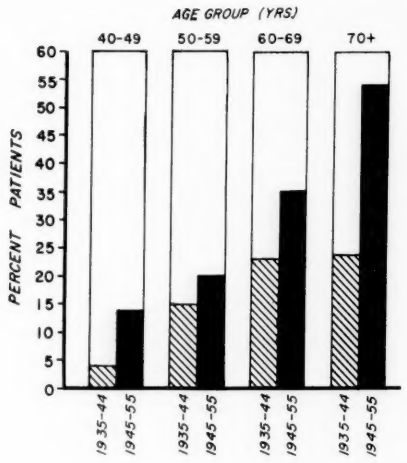

Fig. 1.—Prevalence of advanced coronary atherosclerotic blockage among white males by age groups in an autopsy population, 1935-1944 versus 1945-1955.*

autopsy prevalence of coronary atherosclerosis, in what is believed to be an appropriate sample of the general population, definitely has increased. These differences in the prevalence of coronary atherosclerotic blockage during the two periods of time were statistically significant for every age group, except 50-59.

The hypothesis that coronary atherosclerosis is an inevitable consequence of aging was tested by arranging the accident-cancer records in four age groups: 40-49; 50-59; 60-69; and 70 or over. As seen in Table III, the percentage of persons free of macroscopic coronary atherosclerosis declines with advancing age. The severity of coronary atherosclerosis, furthermore, increased with age. The percentage of persons with 50 or more per cent blockage increased from 9 to 18 to 28 to 47 for the age groups 40-49, 50-59, 60-69, and 70 or more, respectively. Factors other than age must be involved, since 12 per cent of the people 70 or more years of age at the time of death were reported free of macroscopic atherosclerosis.

Another hypothesis tested was that hypertension is associated with the development of coronary atherosclerosis. The accident-cancer victims' records were arranged in four age groups and the records listing hypertension were separated from those in which no hypertension was listed. Table IV points out that more nonhypertensive patients were free of coronary atherosclerosis than were patients with hypertension. The differences were significant at the $p = <0.05$ level for every age group except 60-69. Grade II and III (50 to 99 per cent) blockages, when combined, show that hypertensive patients, especially in the older age groups, developed more advanced atherosclerotic blockage than did nonhypertensive patients. Also, Grade IV (100 per cent) blockage was more frequent among hypertensive patients than among nonhypertensive patients in the 60-69 and the 70 and over age groups. These findings seem to confirm the hypothesis

*Advanced athosclerotic blockage is 50 to 100 per cent blockage of one or more coronary arteries.

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TABLE III. RELATIONSHIP OF CORONARY ARTERY ATHEROSCLEROTIC BLOCKAGE TO AGE BASED ON FINDINGS AMONG ACCIDENT AND CANCER PATIENTS IN AN AUTOPSY POPULATION

AGE GROUP (YEARS)	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE										TOTAL	
	0		I		II		III		IV			
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	77	54	54	38	8	6	3	2	1	<1	143	100
50–59	90	35	123	47	26	10	18	7	2	1	259	100
60–69	50	18	151	54	39	14	29	10	12	4	281	100
70+	32	12	112	41	75	28	38	14	13	5	270	100
Total	249	26	440	46	148	16	88	9	28	3	953	100

TABLE IV. RELATIONSHIP OF HYPERTENSION TO CORONARY ATHEROSCLEROTIC BLOCKAGE BASED ON FINDINGS IN CANCER AND ACCIDENT PATIENTS

AGE (YEARS)	HYPER-TENSION	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE										TOTAL	
		0		I		II		III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	Present	3	25	7	59	1	8	0	0	1	8	12	100
	Absent	74	57	47	36	7	5	3	2	0	0	131	100
50–59	Present	9	21	27	61	5	11	3	7	0	0	44	100
	Absent	81	38	96	45	21	10	15	7	2	1	215	100
60–69	Present	10	15	27	40	11	16	14	21	5	8	67	100
	Absent	40	19	124	58	28	13	15	7	7	3	214	100
70+	Present	5	6	33	37	28	32	16	18	6	7	88	100
	Absent	27	15	79	43	47	26	22	12	7	4	182	100
Total	Present	27	13	94	44	45	21	33	16	12	6	211	100
	Absent	222	30	346	47	103	14	55	7	16	2	742	100

Results:	AGE GROUP	p
(When Grades II and III are combined into one group)	40-49	< 0.01 but > 0.001
	50-59	< 0.20 but > 0.10
	60-69	< 0.01 but > 0.001
	70+	< 0.05 but > 0.02

that hypertension accelerates the development of coronary atherosclerosis in human beings.

Obesity is thought to accelerate atherosclerosis in the coronary arteries, whereas, the underweight condition is thought to impede the development of coronary atheroma. While there are objections to using autopsy data to evaluate the effects of body weight on various conditions, the following analyses were carried out. On the basis of the Metropolitan Life Insurance Company data for the

average weights of white males over the age of 25 years, the records of accident-cancer patients were divided into those 15 per cent or more overweight, those 15 per cent or more underweight, and those in the average range of weights. Then the records were grouped according to age. Table V presents the relationship of body weight to the prevalence of coronary atherosclerosis. Underweight patients in the 40-49, 50-59, and 60-69 age groups had a higher percentage of individuals entirely free of coronary atheroma than did the overweight individuals. This finding was not true at the ages of 70 or more. Grade II and Grade III coronary atherosclerotic blockages were combined to represent advanced atherosclerosis. This degree of advanced atherosclerosis occurred more often among overweight and average-weight than among underweight individuals in the 50-59, 60-69, and 70 and over age groups.

TABLE V. RELATIONSHIP OF BODY WEIGHT AT TIME OF DEATH TO CORONARY ATHEROSCLEROTIC BLOCKAGE BASED ON FINDINGS IN ACCIDENT AND CANCER PATIENTS*

AGE (YEARS)	BODY WEIGHT	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE										TOTAL	
		0		I		II		III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	Overweight	14	44	15	47	3	9	0	0	0	0	32	100
	Avg. weight	29	48	28	46	2	3	2	3	0	0	61	100
	Underweight	26	64	11	27	3	7	0	0	1	2	41	100
50–59	Overweight	15	35	20	47	3	7	5	11	0	0	43	100
	Avg. weight	33	30	54	49	17	15	6	5	1	1	111	100
	Underweight	29	46	25	40	6	9	3	5	0	0	63	100
60–69	Overweight	4	8	29	57	7	14	8	15	3	6	51	100
	Avg. weight	27	21	62	48	19	15	15	11	6	5	129	100
	Underweight	15	21	40	56	9	12	6	8	2	3	72	100
70+	Overweight	6	11	22	40	18	33	5	9	4	7	55	100
	Avg. weight	13	10	52	41	35	27	26	20	3	2	129	100
	Underweight	8	12	33	51	16	24	5	8	3	5	65	100

*Body weight based on Metropolitan Life Insurance data for ideal weight of white males over the age of 25, with a medium body frame.

Overweight = 15 per cent or more above average range.

Average weight = within the limits of the average range or from 14 per cent overweight through 14 per cent underweight.

Underweight = 15 per cent or more under the average range of body weight.

The records were also examined by comparing all records of overweight individuals with those of all nonoverweight (average plus underweight) persons and testing for those with and those without coronary atherosclerosis. Significantly fewer overweight males, aged 60-69, were free of coronary atherosclerosis than were nonoverweight males in the same age group. None of the other age groups showed significant differences in the presence or absence of coronary atherosclerosis.

When records of underweight versus all nonunderweight (overweight plus

average weight) men were similarly tested for the presence of coronary atherosclerosis, a statistically significant difference was found at ages 50-59, where underweight males were more likely to be entirely free of coronary atherosclerosis than were nonunderweight males. This finding did not hold true for the other age groups.

Next, the records of overweight persons were contrasted with those of the underweight by applying the chi-square test to Grade 0, I, II-III, and IV blockage. No significant differences were found. On the other hand, when the records of overweight persons were compared with those for the underweight for the presence or absence of coronary atherosclerosis, a p value of <0.05 was found for ages 60-69. Fewer overweight individuals aged 60-69, therefore, were entirely free of coronary atherosclerosis than were underweight individuals in the same age group.

The effects of body weight on the production of coronary atherosclerotic blockage are thus not manifested before the fifth and sixth decades of life. Body weight would not appear to be as important a factor as hypertension in the production of coronary atherosclerotic blockage. Unfortunately, there were not enough records in the underweight and the overweight categories to separate the effects of body weight from those of hypertension.

DISCUSSION

During the 21 year period, 1935-1955, there was an increase in both the autopsy frequency and the autopsy incidence of ischemic heart disease. The autopsy incidence of ischemic heart disease among white males 40 or more years of age for 1935-1944 was 11.66 per 100 autopsies. This incidence increased to 16.98 per 100 autopsies for the period 1945-1955. What does this mean? Of course, the easiest interpretation is that the incidence of the disease actually has increased. However, let us examine these findings more critically. One factor which could account for the increase is a greater awareness of and improved diagnosis of ischemic heart disease in more recent years. There is no evidence to indicate that observer bias among the various pathologists over the 21 year period could account for this difference in incidence. The autopsy descriptions of the heart and coronary arteries were just as complete for 1935-1944 as they were for 1945-1955. The method of examining the coronary arteries and of recording the results remained consistent. Moreover, more than one pathologist reviewed the findings in each autopsy. There appeared to be no overstatement or understatement of coronary artery disease, and the coronary arteries of persons who died of noncardiovascular causes were described as completely as the coronary arteries of those who died of cardiovascular diseases. Therefore, improved pathologic diagnosis in more recent times could not account for the increased incidence of ischemic heart disease in this autopsy population.

Other possible explanations for the increased autopsy incidence of ischemic heart disease are various antemortem and postmortem selection factors. There is no easy way to estimate the factors which may have determined patients' admissions to the hospital over a period of years. Perhaps ischemic heart disease

was treated more often in the home than in the hospital during the earlier years covered by this study. Usually an autopsy population is more biased than a hospital population, because every person who dies in the hospital does not come to autopsy. However, it is doubtful that the postmortem selection factors for admission to the autopsy population have changed much over the years at this hospital. The annual percentage of autopsies at the New Haven Hospital from 1935 through 1955 has ranged from 47 to 71 per cent, with an average of about 59 per cent per year. From 1935 through 1944 it averaged 62 per cent and from 1945 through 1955 it averaged 57 per cent. During these periods of time autopsies were performed on approximately 75 to 80 per cent of all patients who died with a clinical diagnosis of ischemic heart disease. Although there is no way to be absolutely certain, it seems likely that the increased autopsy incidence of ischemic heart disease reflects an "actual" increase in the incidence of this disease.

A striking finding in this study was that the autopsy prevalence of coronary atherosclerotic blockage increased from 1935-1944 to 1945-1955. The highest ratio was found in the younger patients, aged 40-49, which confirms the findings of Saphir and his associates.[12] This observation also suggests that the factors producing coronary atherosclerosis exerted their greatest atherogenic influence during the last 45 to 55 years. Taking the individuals who died at ages 40-49 (average 45) years, one can reason that this change took place sometime between birth and death or in the period from about 1900-1910 to 1945-1955. The group of patients with the next greatest change in the prevalence of advanced atherosclerosis were those 70 or more years of age. That the second highest change in prevalence occurred in this age group suggests that they were exposed to the atherogenic agents for a longer period of time than persons in the 50-59 and the 60-69 age groups. The race, age, and sex of these individuals are matched and adjustments were made for hypertension and obesity, so other factors, probably environmental ones, produced these atherogenic changes. It seems unlikely that genetic changes in the population could have contributed much to this rather sudden increase in the prevalence of atherosclerosis. These atherogenic effects could have been produced by multiple and possibly additive changes in man's biologic, physical, chemical, and social environment. The important finding is that there has been an increase in the prevalence and severity of coronary atherosclerosis.

The only other study of this kind in the literature is that of Morris.[13] He studied the necropsy records at the London Hospital and reported an increased autopsy incidence of coronary heart disease, but an unexpected decline in the prevalence of advanced coronary atherosclerosis. Since the findings of this study conflict with his findings, the methodology used by Morris will be discussed in detail. He selected "calcification" in the atheroma to indicate "advanced atheroma of protracted and/or severe degeneration." Also included in the "advanced" category were cases described merely as severe and those with ulceration, hemorrhage, stenosis, and occlusion when no calcification was reported. Perhaps his choice of calcification of the atheroma represents a historical residual of English pathology in which "ossified" and "pipestem" coronary arteries were considered important in the etiology of coronary disease. Calcification may have nothing

to do with the "severity" of coronary atherosclerosis in producing ischemic heart disease. It neglects the all-important changes in the vessel lumen. Few American studies of ischemic heart disease even mention calcification of atheroma, much less assign it any importance in the production of clinical disease. Gould[15] stated that calcification of atheromatous plaques is rare before the age of 40. Moreover, extensive calcification of the coronary arteries detectable during life by radiographic films was not found to be associated with clinical coronary heart disease.[16,17] Therefore, the Morris method of classifying the coronary arteries does not seem to be the most suitable one.

Perhaps the greatest source of bias in the Morris study was his choice of cases to represent the prevalence of coronary atherosclerosis in the general population. He divided the autopsy population into three segments: "(A) deaths from coronary heart disease; (B) deaths from conditions associated with coronary disease, especially hypertension (with or without chronic nephritis) and its complications, deaths from arterial degeneration in other sites, and cases with diabetes; and (C) deaths from other conditions, the remainder, and great majority of necropsies. Deaths from a wide variety of conditions—malignant disease—infections, injuries and operations, rheumatic and pulmonary heart disease, etc."[13] Morris assumes that there is no particular association between coronary atheroma and all of the cases in category C, and that any disease groups associated (positively or negatively) with coronary atheroma will tend to cancel each other out. I am in agreement with Morris when he states, "This is certainly a big assumption." Very likely the cases in category C produced an erroneous conclusion.

The prevalence of coronary atherosclerosis increases with age. However, aging is not always associated with atherosclerosis. As seen in Table III, at ages 40-49 about 46 per cent of white males had coronary atherosclerosis and this increased progressively until age 70 or more when 88 per cent of these individuals had atherosclerosis. Twelve per cent of individuals 70 or more years of age were reported free of macroscopic coronary atherosclerosis. Other studies[18,19] confirm the fact that the prevalence of coronary atherosclerosis increases with age.

The association of hypertension with coronary atherosclerosis appears to be straightforward. Persons with hypertension more frequently exhibited coronary atherosclerosis than did nonhypertensive persons in every age group. Also, hypertensive patients had more severe coronary atherosclerotic blockage than nonhypertensive patients. In almost all instances a blood pressure reading was listed on the autopsy protocol in the summary of the patient's clinical history. Hypertension in this study was defined as a blood pressure reading above 150, systolic, and/or 90, diastolic. There was no way to determine how long these autopsy patients had hypertension, whether a diagnosis of hypertension was made prior to admission to the hospital, or the conditions under which the blood pressure readings were taken. Many investigators[20-22] feel that hypertension is an important factor in the development of coronary atherosclerosis. Furthermore, animal experiments confirm the observation that hypertension increases the severity of atherosclerosis.[23] The arbitrarily selected blood pressure readings above 150, systolic, and/or 90, diastolic, may not have been the most suitable

criteria to indicate hypertension. The criteria for the normal range of blood pressures suggested by Master, Dublin, and Marks[24] might have proved a more reliable way to determine the effect of blood pressure on coronary atherosclerosis. If one accepts the limitations of the diagnosis of hypertension as reported on the autopsy protocols, however, then hypertension is definitely associated with an increased prevalence of coronary atherosclerosis.

The relationship of body weight to atherogenesis was not altogether clear. Several serious difficulties arise in studying this relationship in an autopsy population. First, the individuals being studied were those who died of accidental causes and cancer. The body weights used were those recorded at autopsy. Probably the body weight of accident victims was not changed by their cause of death, but this is not true of cancer patients. Many of these patients were emaciated as a result of their malignant disease, so that body weight at time of death did not reflect their weight status throughout most of life. Second, there is a lack of standards for the normal range of body weights. Although the Metropolitan Life Insurance Company weight tables leave a lot to be desired, the crudeness of the autopsy weight measurements did not seem to warrant a more refined weight evaluation system. Third, it was not possible in this study to separate the effects of obesity from those of hypertension, because of the limited number of overweight individuals. An increase in body weight has been shown to increase the systolic and diastolic blood pressures.[25,26] However, if obesity is a factor in atherogenesis, it certainly appears not to be as important as hypertension.

SUMMARY

1. An epidemiologic study, based on the findings in 2,731 white males 40 or more years of age on whom autopsies were performed at the Grace–New Haven Community Hospital, New Haven, Connecticut, from 1935 through 1955, showed that the autopsy incidence of ischemic heart disease increased over the 21 year period of time. The rate per 100 autopsies increased from 11.66 for the period, 1935-1944, to 16.98 for the period, 1945-1955.

2. The autopsy records of accident victims and cancer patients were pooled to form a group of records of persons whose coronary arteries were thought to be reasonably representative of the coronary arteries of the general population. On the basis of these records, the autopsy prevalence of coronary atherosclerosis increased from 1935-1944 to 1945-1955. A higher percentage of patients in every age group was entirely free of coronary atherosclerosis in 1935-1944 than in 1945-1955. Furthermore, the prevalence of advanced (50 to 100 per cent) coronary atherosclerotic blockage was higher during the latter period, 1945-1955. The ratios of cases of advanced atherosclerosis in 1935-1944 compared with 1945-1955 were: 1 to 3.5 at ages 40-49; 1 to 1.3 at ages 50-59; 1 to 1.5 at ages 60-69; and 1 to 2.3 at ages 70 or more. It was concluded that there has been a "real" rather than an "apparent" increase in the incidence of ischemic heart disease and in the prevalence of coronary atherosclerosis.

3. The prevalence of coronary atherosclerosis increased with age. The percentage of patients showing macroscopic evidence of coronary atherosclerosis

increased from 46 at ages 40-49 to 65 at ages 50-59 to 82 at ages 60-69, to 88 at age 70 or more.

4. Hypertension was found to affect the development of coronary atherosclerosis. The percentage of nonhypertensive patients versus hypertensive patients with coronary atherosclerosis by age groups were: 43 versus 75 at ages 40-49; 62 versus 79 at ages 50-59; 81 versus 85 at ages 60-69; and 85 versus 94 at age 70 or more. The atherogenic effects of obesity were not as straightforward as those of hypertension. Because of inherent limitations in the use of autopsy data, no conclusions could be reached about the association between body weight and coronary atherosclerosis.

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EPIDEMIOLOGY OF ISCHEMIC HEART DISEASE AMONG WHITE MALES

III. Role of Coronary Atherosclerosis and Clot Formation in Patients With Ischemic Heart Disease

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ALTHOUGH there have been many pathologic studies of ischemic heart disease in the past, there have been few epidemiologic studies of this disease in autopsy populations. Epidemiologic methods and techniques have been recommended for studying ischemic heart disease by several prominent investigators.[1-5] Autopsy records provide more accurate diagnostic information than clinical records, death certificates, and laboratory studies.[6,7] Whereas most pathologic studies of ischemic heart disease have been descriptive in nature, the present epidemiologic study attempts to test hypotheses about ischemic heart disease based on pathologic findings in an autopsy population.

The purpose of this investigation is to compare the coronary arteries of patients with ischemic heart disease with the coronary arteries of a "control" group of patients in an autopsy population thought to be reasonably representative of the general population, to ascertain whether or not the basic pathology of ischemic heart disease has changed during a 21 year period, to determine the relationship of coronary atherosclerosis and coronary clot formation to ischemic heart disease, and to study other factors associated with the latter. In a review of the available literature, no report was found in which the coronary arteries of patients with ischemic heart disease were compared with those of a suitable "control" group of patients.

MATERIALS AND METHODS

This study is based on the pathologic findings in white males 40 or more years of age on whom autopsies were performed at the Grace–New Haven Community Hospital, New Haven, Connecticut, from 1935 through 1955.

This portion of the study is concerned with three categories of patients: (1) accident and cancer victims; (2) patients with relatively typical ischemic heart disease; and (3) patients with ischemic heart disease and concomitant diabetes mellitus. Accident victims' coronary arteries were thought to be reasonably representative of the coronary arteries of the general population. No

This paper is based on a study of the epidemiology of ischemic heart disease in partial fulfillment of the requirements for the degree of Doctor of Public Health from Yale University School of Medicine, New Haven, Conn.

difference in the severity of coronary atherosclerosis or the presence of coronary clots was found when cancer victims were compared with accident victims. It was felt that the combined accident-cancer group was the group in the autopsy population whose coronary arteries would be most representative of the coronary arteries of the general population. Therefore, the records of accident-cancer patients were used as a control group to compare with those of patients who had ischemic heart disease.

Ischemic heart disease was defined as any case in which one or more of the following conditions was listed: coronary thrombosis, coronary occlusion, coronary occlusion due to atherosclerosis, myocardial infarction, angina pectoris, and coronary insufficiency. Any patient having one or more of these conditions and concomitant diabetes mellitus was not included in this group of relatively typical ischemic heart disease patients. There was reason to believe that the pathologic findings in their coronary arteries might be different. Therefore, patients with ischemic heart disease and concomitant diabetes mellitus were treated as a separate group.

The coronary arteries of these patients were classified according to the amount of atherosclerotic blockage in the most severely diseased coronary artery or one of its major branches as described in the autopsy protocol. Also, the presence or absence of a coronary artery clot was noted. A more detailed description of this classification, evidence of its validity, and the techniques used for matching the records were presented in the first portion of this study.[8] In addition, criteria used for assigning patients' records to hypertension versus no hypertension groups and to overweight, average-weight, and underweight categories have been discussed elsewhere.[8]

RESULTS

Has the pathology of ischemic heart disease changed over the years? The hypothesis that patients with ischemic heart disease have more clot-producing coronary blockage now than formerly was tested by dividing the records into two periods of time, 1935-1944 and 1945-1955, and arranging them according to age at death (Table I). The findings suggest that there may have been relatively more clots producing ischemic heart disease among young patients during the latter period of time but these differences were not statistically significant.

The hypothesis that coronary atherosclerotic blockage is less severe among ischemic heart disease patients now than formerly was tested in a similar manner. The records of these patients were divided into two periods of time, 1935-1944 and 1945-1955, and arranged into age groups. As seen in Table II, a higher percentage of patients in every age group had Grade IV (100 per cent) atherosclerotic blockage during 1935-1944 than during 1945-1955. Also, a higher percentage of patients during the earlier period of time, 1935-1944, had 90 per cent or more atherosclerotic blockage (Grades III and IV). This finding was true for every age group except 60-69. When the chi-square test was applied to Grade I, II, III, and IV blockage by age groups for 1935-1944 versus 1945-1955, a statistically significant difference was found for every age group except 40-49.

TABLE I. COMPARISON OF CORONARY ARTERY CLOTS AMONG PATIENTS WITH ISCHEMIC HEART DISEASE, BY AGE GROUPS, DURING 1935-1944 VERSUS 1945-1955

AGE GROUP	PERIOD OF TIME	CORONARY ARTERY CLOT				TOTAL	
		PRESENT		ABSENT			
		NO.	%	NO.	%	NO.	%
40–49	1935–1944	9	50	9	50	18	100
	1945–1955	16	57	12	43	28	100
50–59	1935–1944	17	43	23	57	40	100
	1945–1955	33	57	25	43	58	100
60–69	1935–1944	27	54	23	46	50	100
	1945–1955	52	55	43	45	95	100
70+	1935–1944	19	53	17	47	36	100
	1945–1955	36	49	37	51	73	100
Total	1935–1944	72	50	72	50	144	100
	1945–1955	137	54	117	46	254	100

Results:

AGE GROUP	p
40-49	< 0.70 but > 0.50
50-59	< 0.20 but > 0.10
60-69	< 0.95 but > 0.90
70+	< 0.80 but > 0.70

How do the coronary arteries of patients with ischemic heart disease differ from the coronary arteries of persons in the general population? Table III shows a comparison of the severity of coronary atherosclerotic blockage among accident-cancer patients and ischemic heart disease patients. As expected, the ischemic heart disease group exhibited far more advanced atherosclerotic blockage than did the control group. Twenty per cent of the heart disease patients versus 3 per cent of the accident-cancer patients had Grade IV (100 per cent) atherosclerotic blockage. Grade II and III blockage (50 to 99 per cent) combined included 75 per cent of the ischemic heart disease patients versus 25 per cent of the accident-cancer patients. Every patient who died of ischemic heart disease had some atherosclerosis present, whereas 26 per cent of the total control group were reported free of macroscopic atherosclerosis.

Coronary artery clots were also much more prevalent among the ischemic heart disease group than among the accident-cancer group (Table IV). The differences obviously were significant; for the totals a chi-square value of 466.354 and a p value of <0.001 were obtained.

What is the relationship of coronary atherosclerotic blockage to ischemic heart disease? A basic hypothesis is that atherosclerosis is the fundamental pathologic lesion of ischemic heart disease. Yet it is a well-known fact that not every patient with coronary atherosclerosis develops ischemic heart disease. In Table III one finds that every patient with ischemic heart disease had atherosclerotic

TABLE II. PREVALENCE OF VARIOUS GRADES OF CORONARY ATHEROSCLEROTIC BLOCKAGE AMONG PATIENTS WITH ISCHEMIC HEART DISEASE, BY AGE GROUPS, FOR 1935-1944 AND 1945-1955

AGE GROUP	PERIOD OF TIME	GRADE ATHEROSCLEROTIC BLOCKAGE								TOTAL	
		I		II		III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	1935–1944	2	11	2	11	10	56	4	22	18	100
	1945–1955	0	0	9	32	17	61	2	7	28	100
50–59	1935–1944	2	5	1	3	25	62	12	30	40	100
	1945–1955	5	9	21	36	20	34	12	21	58	100
60–69	1935–1944	3	6	11	22	18	36	18	36	50	100
	1945–1955	3	3	19	20	57	60	16	17	95	100
70+	1935–1944	0	0	3	8	27	75	6	17	36	100
	1945–1955	3	4	21	29	39	53	10	14	73	100
Total	1935–1944	7	5	17	12	80	55	40	28	144	100
	1945–1955	11	4	70	28	133	52	40	16	254	100

Results:

AGE GROUP	p
40-49	< 0.10 but > 0.05
50-59	< 0.001
60-69	< 0.05 but > 0.02
70+	< 0.05 but > 0.02

blockage present in one or more coronary arteries. On the other hand, from 12 to 54 per cent of the control group lacked macroscopic coronary atherosclerosis. There appears to be a "critical level" of atherosclerotic blockage which is almost always necessary for the development of ischemic heart disease. For example, 95 per cent of all patients with ischemic heart disease had at least Grade II (50 to 89 per cent) coronary atherosclerotic blockage and 73 per cent of the patients had Grade III or IV (90 to 100 per cent) blockage. The patients with ischemic heart disease (5 per cent) who exhibited less than 50 per cent coronary atherosclerotic blockage may be considered atypical cases. These data would tend to support the hypothesis that coronary atherosclerosis is a necessary factor in the development of ischemic heart disease. However, complete blockage of a coronary artery by atherosclerosis is not a necessary requirement for ischemic heart disease, since only 20 per cent of the patients had Grade IV (100 per cent) blockage.

Although, without exception, every patient with ischemic heart disease had coronary atherosclerosis, only 53 per cent of them had a coronary clot. No patient in the entire autopsy population, regardless of his diagnosis, had a coronary clot unless coronary atherosclerosis also was present. This observation would tend to support the hypothesis that coronary atherosclerosis is the fundamental lesion of ischemic heart disease and that coronary clot formation is dependent on the presence of atherosclerosis.

What is the effect of hypertension on coronary atherosclerosis and coronary clot formation among patients with ischemic heart disease? Table V shows that

TABLE III. COMPARISON OF CORONARY ARTERY ATHEROSCLEROTIC BLOCKAGE AMONG PATIENTS WITH ISCHEMIC HEART DISEASE AND ACCIDENT-CANCER PATIENTS, BY AGE GROUPS

AGE GROUP (YEARS)	DISEASE GROUP	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE										TOTAL	
		0		I		II		III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	Ischemic heart disease	—	—	2	4	11	24	27	59	6	13	46	100
	Accident-cancer	77	54	54	38	8	6	3	2	1	<1	143	100
50–59	Ischemic heart disease	—	—	7	7	22	22	45	46	24	25	98	100
	Accident-cancer	90	35	123	47	26	10	18	7	2	1	259	100
60–69	Ischemic heart disease	—	—	6	4	30	21	75	52	34	23	145	100
	Accident-cancer	50	18	151	54	39	14	29	10	12	4	281	100
70+	Ischemic heart disease	—	—	3	3	24	22	66	60	16	15	109	100
	Accident-cancer	32	12	112	41	75	28	38	14	13	5	270	100
Total	Ischemic heart disease	—	—	18	5	87	22	213	53	80	20	398	100
	Accident-cancer	249	26	440	46	148	16	88	9	28	3	953	100

Results for total: $\chi^2 = 604.680$, d.f. = 4, p = < 0.001.

TABLE IV. PREVALENCE OF CORONARY ARTERY CLOTS AMONG PATIENTS WITH ISCHEMIC HEART DISEASE AND ACCIDENT-CANCER PATIENTS, BY AGE GROUPS

AGE GROUP (YEARS)	DISEASE GROUP	CORONARY ARTERY CLOT				TOTAL	
		PRESENT		ABSENT			
		NO.	%	NO.	%	NO.	%
40–49	Ischemic heart disease	25	54	21	46	46	100
	Accident-cancer	1	1	142	99	143	100
50–59	Ischemic heart disease	50	51	48	49	98	100
	Accident-cancer	3	1	256	99	259	100
60–69	Ischemic heart disease	79	54	66	46	145	100
	Accident-cancer	14	5	267	95	281	100
70+	Ischemic heart disease	55	50	54	50	109	100
	Accident-cancer	13	5	257	95	270	100
Total	Ischemic heart disease	209	53	189	47	398	100
	Accident-cancer	31	3	922	97	953	100

Results for total: $\chi^2 = 466.354$, d.f. = 1, p = < 0.001.

TABLE V. RELATION OF HYPERTENSION TO CORONARY ATHEROSCLEROTIC BLOCKAGE AMONG PATIENTS WITH ISCHEMIC HEART DISEASE, BY AGE GROUPS

AGE GROUP (YEARS)	HYPERTENSION	GRADE CORONARY ATHEROSCLEROTIC BLOCK								TOTAL	
		I		II		III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	Present	1	5	3	17	12	67	2	11	18	100
	Absent	1	4	8	28	15	54	4	14	28	100
50–59	Present	4	10	7	18	19	49	9	23	39	100
	Absent	3	5	15	25	26	44	15	26	59	100
60–69	Present	3	4	14	20	34	50	18	26	69	100
	Absent	3	4	16	21	41	54	16	21	76	100
70+	Present	2	4	12	21	34	62	7	13	55	100
	Absent	1	2	12	22	32	59	9	17	54	100
Total	Present	10	5	36	20	99	55	36	20	181	100
	Absent	8	4	51	23	114	53	44	20	217	100

Results: No significant difference between hypertensive and nonhypertensive patients.

there was no essential difference in the severity of coronary atherosclerotic blockage among ischemic heart disease patients with and without hypertension. On the other hand, Table VI demonstrates that hypertension had a pronounced association with coronary clot formation among ischemic heart disease patients. Fewer coronary clots developed in hypertensive patients than in nonhypertensive patients in every age group. For the totals, this difference was statistically significant ($p = <0.01$).

Body weight at the time of death had no significant effect on the severity of coronary atherosclerotic blockage among ischemic heart disease patients. Table VII shows no clear-cut relationship among those overweight, underweight, and of average weight in so far as atherosclerotic blockage was concerned. However, body weight had a striking association with the development of coronary artery clots (Table VIII). A general trend is seen throughout this table, namely, that overweight patients had the highest percentage of clots, that average weight patients had the next highest percentage of clots, and that underweight patients had the lowest percentage of clots. There were too few underweight individuals in the 40-49 and 50-59 age groups for proper analyses. However, for the "total" row in Table VIII, clots were present in 62 per cent of the overweight, in 48 per cent of those of average weight, and in 27 per cent of the underweight ischemic heart disease patients. These differences were statistically significant at the $p = <0.001$ level.

Why do some ischemic heart disease patients exhibit coronary atherosclerosis without clots while others show coronary atherosclerosis with clots? In this study 53 per cent of the ischemic heart disease patients had coronary artery clots.

TABLE VI. RELATIONSHIP OF HYPERTENSION TO CORONARY ARTERY CLOT FORMATION AMONG PATIENTS WITH ISCHEMIC HEART DISEASE, BY AGE GROUPS

AGE GROUP (YEARS)	HYPERTENSION	CORONARY ARTERY CLOT				TOTAL	
		PRESENT		ABSENT			
		NO.	%	NO.	%	NO.	%
40–49	Present	8	44	10	56	18	100
	Absent	17	61	11	39	28	100
50–59	Present	18	46	21	54	39	100
	Absent	32	54	27	46	59	100
60–69	Present	30	43	39	57	69	100
	Absent	49	64	27	36	76	100
70+	Present	24	44	31	56	55	100
	Absent	31	57	23	43	54	100
Total	Present	80	44	101	56	181	100
	Absent	129	59	88	41	217	100

Results:

AGE GROUP	p
40-49	< 0.30 but > 0.20
50-59	< 0.50 but > 0.30
60-69	< 0.02 but > 0.01
70+	< 0.20 but > 0.10
Total	< 0.01 but > 0.001

Perhaps these patients have an abnormality of the coagulation mechanism. Many such patients die of complications of blood coagulation, namely, embolism and thrombosis. A comparison of "extracardiac" clots among ischemic heart disease patients and cancer patients might provide a clue about the presence or absence of a coagulation defect. Clots in the heart vessels, chambers, and muscles were excluded, since they were considered to result from the local disease process. Only extracardiac clots were counted for the two groups of patients. Cancer victims were used for this comparison because cancer patients and ischemic heart disease patients, for the most part, have been bed patients suffering from chronic diseases. As can be seen in Table IX, a higher percentage of ischemic heart disease patients in every age group had extracardiac clots. These differences were statistically significant for every age group except 60-69. These findings would tend, indirectly, to support the hypothesis that ischemic heart disease patients have abnormal coagulation which promotes intravascular clotting.

On the basis of these findings, the hypothesis was developed that ischemic heart disease patients with coronary artery clots develop more extracardiac clots than do ischemic heart disease patients without coronary artery clots. The results of this analysis are presented in Table X. No significant difference was found in the prevalence of extracardiac clots among the two groups of patients.

Throughout this study diabetes mellitus was treated as a separate disease entity. Since diabetic persons develop coronary and peripheral atherosclerosis

TABLE VII. RELATIONSHIP OF BODY WEIGHT AT TIME OF DEATH TO THE SEVERITY OF CORONARY ATHEROSCLEROTIC BLOCKAGE AMONG PATIENTS WITH ISCHEMIC HEART DISEASE, BY AGE GROUPS*

AGE GROUP (YEARS)	BODY WEIGHT†	GRADE CORONARY ATHEROSCLEROTIC BLOCKAGE								TOTAL	
		I		II		III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
40–49	Overweight	1	6	5	31	8	50	2	13	16	100
	Avg. weight	3	8	8	22	22	59	4	11	37	100
	Underweight	—	—	—	—	1	33	2	67	3	100
50–59	Overweight	2	5	11	28	17	44	9	23	39	100
	Avg. weight	4	7	12	20	28	46	16	27	60	100
	Underweight	—	—	—	—	3	75	1	25	4	100
60–69	Overweight	5	7	19	27	31	44	16	22	71	100
	Avg. weight	2	2	15	15	54	56	26	27	97	100
	Underweight	1	8	2	17	5	42	4	33	12	100
70+	Overweight	1	3	12	33	18	50	5	14	36	100
	Avg. weight	2	2	17	19	54	61	16	18	89	100
	Underweight	1	4	5	20	12	48	7	28	25	100
Total	Overweight	9	5	47	29	74	46	32	20	162	100
	Avg. weight	11	4	52	18	158	56	62	22	283	100
	Underweight	2	4	7	16	21	48	14	32	44	100

Results: No significant difference between weight groups.

*Additional cases of ischemic heart disease were collected from other disease groups, excluding diabetes, to bring out the effect of the underweight condition.

†Body weight based on Metropolitan Life Insurance Company data for white males over the age of 25, with a medium body frame.

Overweight = 15 per cent or more above average range.

Average weight = average range, or from 14 per cent overweight through 14 per cent underweight.

Underweight = 15 per cent or more under average range.

more frequently and at an earlier age than do the nondiabetic, the hypothesis was entertained that diabetic patients with ischemic heart disease have relatively more severe coronary atherosclerotic blockage than do those who are not diabetic. Table XI shows that those with concomitant diabetes had more advanced coronary atherosclerotic blockage than did patients without diabetes.

The fact that ischemic heart disease patients with concomitant diabetes mellitus had more advanced coronary atherosclerotic blockage than those without diabetes suggested that perhaps those with diabetes developed fewer coronary clots. This hypothesis was tested and the results may be found in Table XII. Unfortunately, there were too few such patients in the 40-49 and 50-59 age groups for meaningful age-specific analyses. However, throughout this table it is apparent that the diabetic patients developed fewer coronary clots. These data suggest that the pathology of ischemic heart disease among diabetics differs from the usual pattern found among the nondiabetic.

DISCUSSION

Most previous studies of ischemic heart disease in autopsy populations have

TABLE VIII. RELATIONSHIP BETWEEN BODY WEIGHT AT TIME OF DEATH AND CORONARY ARTERY CLOT FORMATION IN PATIENTS WITH ISCHEMIC HEART DISEASE, BY AGE GROUPS*

AGE GROUP (YEARS)	BODY WEIGHT†	CORONARY ARTERY CLOT				TOTAL	
		PRESENT		ABSENT			
		NO.	%	NO.	%	NO.	%
40–49	Overweight	11	69	5	31	16	100
	Avg. weight	21	57	16	43	37	100
	Underweight	—	—	3	100	3	100
50–59	Overweight	25	64	14	36	39	100
	Avg. weight	29	48	31	52	60	100
	Underweight	2	50	2	50	4	100
60–69	Overweight	44	62	27	38	71	100
	Avg. weight	44	45	53	55	97	100
	Underweight	1	8	11	92	12	100
70+	Overweight	21	58	15	42	36	100
	Avg. weight	43	48	46	52	89	100
	Underweight	9	36	16	64	25	100
Total	Overweight	101	62	61	38	162	100
	Avg. weight	137	48	146	52	283	100
	Underweight	12	27	32	73	44	100

Results for total: $\chi^2 = 19.049$, d.f. = 2, $p = < 0.001$.

*Additional cases of ischemic heart disease were collected from other disease groups, excluding diabetes, to bring out the effect of the underweight condition.

†Body weight based on Metropolitan Life Insurance Company data for white males over the age of 25, with a medium body frame.

Overweight = 15 per cent or more above average range.

Average weight = average range or from 14 per cent overweight through 14 per cent underweight.

Underweight = 15 per cent or more under average range.

been descriptive in nature. For example, comparisons were made of the autopsy incidence and the age, sex, and race distributions of ischemic heart disease patients. The present study differs from previous pathologic studies of ischemic heart disease in that hypotheses about the disease are tested. It is generally accepted that pathologic diagnoses are more accurate than most other sources of diagnostic information. However, epidemiologists have been rather reluctant to utilize necropsy populations for studies because, in many instances, they are biased populations.[10] There is an urgent need to develop suitable biostatistical techniques to adjust for these antemortem and postmortem biases so that necropsy data may be used for epidemiologic studies. It is also important in autopsy studies that hypothesis testing be placed on equal footing with descriptive accounts of disease. Many valuable data about the etiology of diseases lie dormant in autopsy files because autopsy populations have not been utilized fully for epidemiologic studies.

The incidence of ischemic heart disease and the prevalence of coronary atherosclerotic blockage among accident and cancer patients increased from 1935-1944 to 1945-1955 in this autopsy population.[9] Since Herrick's reports

TABLE IX. PREVALENCE OF EXTRACARDIAC CLOTS AMONG CANCER PATIENTS AND PATIENTS WITH ISCHEMIC HEART DISEASE AT AUTOPSY, BY AGE GROUPS

AGE GROUP (YEARS)	DISEASE GROUP	EXTRACARDIAC CLOT				TOTAL	
		PRESENT		ABSENT			
		NO.	%	NO.	%	NO.	%
40–49	Heart disease	14	30	32	70	46	100
	Cancer	13	15	74	85	87	100
50–59	Heart disease	35	36	63	64	98	100
	Cancer	37	18	171	82	208	100
60–69	Heart disease	47	32	98	68	145	100
	Cancer	58	24	184	76	242	100
70+	Heart disease	40	37	69	63	109	100
	Cancer	53	23	174	77	227	100
Total	Heart disease	136	34	262	66	398	100
	Cancer	161	21	603	79	764	100

Results:

AGE GROUP	p
40-49	< 0.05 but > 0.02
50-59	< 0.001
60-69	< 0.10 but > 0.05
70+	< 0.02 but > 0.01
Total	< 0.001

TABLE X. PREVALENCE OF EXTRACARDIAC CLOTS AMONG ISCHEMIC HEART DISEASE PATIENTS WITH AND WITHOUT CORONARY ARTERY CLOTS, BY AGE GROUPS

AGE GROUP (YEARS)	CORONARY CLOT	EXTRACARDIAC CLOTS				TOTAL	
		PRESENT		ABSENT			
		NO.	%	NO.	%	NO.	%
40–49	Present	6	24	19	76	25	100
	Absent	8	38	13	62	21	100
50–59	Present	16	32	34	68	50	100
	Absent	19	40	29	60	48	100
60–69	Present	22	28	57	72	79	100
	Absent	25	38	41	62	66	100
70+	Present	21	38	34	62	55	100
	Absent	19	35	35	65	54	100
Total	Present	65	31	144	69	209	100
	Absent	71	38	118	62	189	100

Results: No significant difference between patients with and without coronary artery clots.

TABLE XI. GRADES OF CORONARY ARTERY ATHEROSCLEROTIC BLOCKAGE AMONG ISCHEMIC HEART DISEASE PATIENTS WITH AND WITHOUT CONCOMITANT DIABETES MELLITUS, BY AGE GROUPS

AGE GROUP (YEARS)	DIABETES MELLITUS	GRADE ATHEROSCLEROTIC BLOCKAGE						TOTAL	
		I		II AND III		IV			
		NO.	%	NO.	%	NO.	%	NO.	%
40–49	Absent	2	4	38	83	6	13	46	100
	Present	–	–	1	50	1	50	2	100
50–59	Absent	7	7	67	68	24	25	98	100
	Present	–	–	9	69	4	31	13	100
60–69	Absent	6	4	105	72	34	24	145	100
	Present	–	–	14	67	7	33	21	100
70+	Absent	3	3	90	82	16	15	109	100
	Present	–	–	11	61	7	39	18	100
Total	Absent	18	5	300	75	80	20	398	100
	Present	–	–	35	65	19	35	54	100

Results for total: $\chi^2 = 8.203$, d.f. = 2, p = < 0.02 but > 0.01.

TABLE XII. PREVALENCE OF CORONARY ARTERY CLOTS AMONG ISCHEMIC HEART DISEASE PATIENTS WITH AND WITHOUT CONCOMITANT DIABETES MELLITUS, BY AGE GROUPS

AGE GROUP (YEARS)	DIABETES MELLITUS	CORONARY ARTERY CLOT				TOTAL	
		PRESENT		ABSENT			
		NO.	%	NO.	%	NO.	%
40–49	Absent	25	54	21	46	46	100
	Present	—	—	2	100	2	100
50–59	Absent	50	51	48	49	98	100
	Present	5	38	8	62	13	100
60–69	Absent	79	54	66	46	145	100
	Present	8	38	13	62	21	100
70+	Absent	55	50	54	50	109	100
	Present	7	39	11	61	18	100
Total	Absent	209	53	189	47	398	100
	Present	20	37	34	63	54	100

Results for total: $\chi^2 = 4.609$, d.f. = 1, p = < 0.05 but > 0.02.

of coronary thrombosis in 1912 and 1919,[11,12] this cause of coronary blockage has received a great deal of attention. Indeed, coronary thrombosis has been mentioned so frequently in the medical literature in the last 30 years that one wonders

if there has been an actual increase in this form of coronary blockage. Morris[13] briefly alluded to this possibility. The hypothesis that there has been an increase in the prevalence of coronary clots among patients with ischemic heart disease was tested. There was a "suggestion" that the prevalence of coronary clots had increased among these patients aged 40-49 and 50-59 from 1935-1944 to 1945-1955. However, these differences were not statistically significant.

Relatively less severe coronary atherosclerotic blockage was found to produce ischemic heart disease in 1945-1955 than in 1935-1944. If coronary atherosclerotic blockage per se is a less important factor in ischemic heart disease now than formerly, then some other factor or factors must be involved. There was not a coincidental increase in coronary clots to account for a comparable amount of coronary artery blockage. Perhaps the myocardium was rendered more susceptible to anoxia and infarction by other mechanisms so that relatively less coronary blockage was needed to produce ischemic heart disease. Following Selye's work, Wexler and Miller[14] showed experimentally in rats that corticotropin and stress may be factors in ischemic heart disease. Some of these animals developed myocardial infarcts without extensive coronary atheromatous lesions. On the basis of the evidence presented in this study it seems possible that there has been a gradual change in the relative importance of coronary atherosclerosis and coronary clot formation in the pathogenesis of ischemic heart disease.

Of considerable importance was the finding that all patients with ischemic heart disease had atherosclerotic blockage, while 26 per cent of the control group were reported free of macroscopic atherosclerosis. This finding would tend to incriminate atherosclerosis as a necessary factor in ischemic heart disease and point to it as the primary lesion of the disease. Coronary clots do not appear to be the primary lesion because they were reported in only 53 per cent of the heart disease patients. Also, clots were never found in the absence of atherosclerosis. Studies in pathologic anatomy indicate that clots usually form at the sites of atheromatous plaques and develop secondarily to the atherosclerosis.[15,16]

There appears to be a critical level of coronary atherosclerotic blockage necessary to produce ischemic heart disease for most patients. Ninety-five per cent of the ischemic heart disease patients had 50 per cent or more coronary atherosclerotic blockage, 73 per cent of them had 90 or more per cent blockage, and 20 per cent of them had 100 per cent blockage. The remaining 5 per cent of the ischemic heart disease patients had from 1 to 49 per cent coronary atherosclerotic blockage and they may be considered atypical patients. Of the 18 (5 per cent) atypical patients, 9 had angina pectoris—3 with and 6 without myocardial infarcts. Two of these patients had syphilitic heart disease with aortic valvulitis and 2 had rheumatic heart disease with valvulitis. One patient had recurrent paroxysmal tachycardia, one patient died of a myocardial infarction possibly resulting from coronary spasm secondary to an impacted gall stone, and one patient developed coronary thrombosis associated with coronary arteritis. Grade I (1 to 49 per cent) atherosclerotic blockage was the only anatomic finding in the remaining 2 patients with myocardial infarcts. Eight of the 18 ischemic heart disease patients with Grade I atherosclerotic blockage had coronary clots. Other investigators[17-20] have reported cases of ischemic heart disease, especially of

angina pectoris, exhibiting few or no changes in the coronary arteries. Various physiologic and pathologic mechanisms have been suggested to explain the findings in these atypical cases of ischemic heart disease.[19,20]

There was no difference in the severity of atherosclerotic blockage among ischemic heart disease patients with and without hypertension. On the other hand, hypertension seemed to retard the development of coronary clots among these patients. Shock or hypotension following an acute myocardial infarction is a poor prognostic sign. Hypotension would tend to reduce the cardiac output and the coronary arterial flow. This slowing of the coronary blood flow would tend to promote thrombosis. Hypertension, on the other hand, would increase the coronary arterial pressure and tend to inhibit thrombosis, all other factors remaining constant. The fact that nonhypertensive patients develop more coronary clots than hypertensive patients might prove important in the clinical management of ischemic heart disease.

Body weight at the time of death was found to have no influence on the severity of coronary atherosclerotic blockage among ischemic heart disease patients. However, body weight had a startling relationship to coronary artery clot formation. Generally, the prevalence of hypertension increases with obesity, but this association of the overweight condition with clot formation could not be due to concomitant hypertension, since hypertension was associated with a decrease in clot formation. That overweight patients with ischemic heart disease developed more coronary clots than those of average weight and those underweight suggests that they may have a defect in their coagulation mechanism.

There have been many attempts to demonstrate measurable coagulation defects among patients with ischemic heart disease, but the results are by no means clear. McDonald and Edgill[22] studied the coagulability of blood in 48 ischemic heart disease patients and in 48 healthy control subjects and reported significant differences in the following tests: thromboplastin generation, platelet stickiness, fibrinogen estimation, and prothrombin time (Russell's viper venom). Friedman and his associates[23] in a study of blood coagulation among accountants found that during periods of stress the serum cholesterol increased along with an acceleration of the blood coagulation time. Keys and co-workers[24] found a significant shortening of the coagulation time in 12 subjects after the ingestion of fatty meals. Other investigators[25-27] give conflicting results concerning shortening of the coagulation time following the ingestion of fatty meals. The findings in this study suggest that perhaps overweight persons may be more prone to a shortening of the coagulation time than those not overweight.

Additional evidence to support the hypothesis that there is a coagulation defect in ischemic heart disease was sought by comparing the prevalence of "extracardiac" clots among ischemic heart disease patients and cancer patients. A higher percentage of ischemic heart disease patients had extracardiac clots in every age group. It may be argued that one would expect to find more thrombi and emboli in heart disease patients because of impaired circulation. Shock, hypotension, and a decreased cardiac output secondary to myocardial infarction would tend to produce stasis of blood, a predisposing factor in intravascular clotting. Also, mural thrombi in the heart chambers would be expected to produce

embolic episodes. Nonetheless, ischemic heart disease patients had more peripheral venous thrombi as well as more peripheral and pulmonary emboli than cancer patients. This indirect evidence tends to support the idea of a coagulation defect, but it certainly does not prove it. Ischemic heart disease patients with coronary clots did not develop more extracardiac clots than did those without coronary clots. As yet there are no simple laboratory tests to predict which patients are likely to develop intravascular clots.[28]

There have been few pathologic studies in which diabetic patients with concomitant ischemic heart disease have been compared with the nondiabetic with ischemic heart disease. Almost all previous studies on the relationship of diabetes mellitus to ischemic heart disease were done in one of two ways: (1) to compare all diabetic patients versus all other (nondiabetic) patients in an autopsy population; or (2) to study the prevalence of ischemic heart disease among a group of diabetic persons. When the grades of coronary atherosclerotic blockage among ischemic heart disease patients with and without concomitant diabetes mellitus were compared, the diabetics were found to have significantly more severe atherosclerotic blockage. Furthermore, coronary clots were less prevalent among diabetics than among nondiabetics with ischemic heart disease. Blotner[29] found coronary thrombosis in 23 per cent of the 35 diabetic patients with ischemic heart disease that he studied. Liebow and Hellerstein[30] noted that diabetics have a higher autopsy incidence of coronary thrombosis than nondiabetics.

The finding in this study that patients with ischemic heart disease and concomitant diabetes mellitus have significantly more severe coronary atherosclerotic blockage and significantly fewer coronary clots than similar patients without diabetes suggests that ischemic heart disease among diabetics may be a different physiochemical and pathologic process than in the nondiabetic. The following evidence seems to support this hypothesis: (1) coronary atherosclerosis develops at an earlier age and is more severe among diabetics[31,32]; (2) ischemic heart disease is more common among diabetics than among nondiabetics; (3) there is a change in the male-female sex ratio of ischemic heart disease from about 3 or 4 to 1 for nondiabetics to about 1 to 1 for diabetics[33,34]; (4) chemical differences have been found in the atheromatous coronary arteries of diabetics[35]; (5) diabetics are more prone to develop other vascular diseases, including Kimmelstiel-Wilson glomerulosclerosis and peripheral vascular disease; and (6) diabetic persons have biochemical, metabolic, and endocrinologic alterations not found in the nondiabetic. Lundbaek and Petersen[35] reported that the coronary arteries of diabetic persons contained less calcium, less lecithin, and more cephalin than the coronary arteries of nondiabetics. Therefore, it would appear that ischemic heart disease among diabetics differs from the disease among nondiabetics. This may represent a variant of the atherogenic process in the coronary arteries or it may indicate a different pathologic process.

SUMMARY

1. An epidemiologic study of ischemic heart disease among white males in a necropsy population showed that the basic pathology of the disease appar-

ently is changing. Ischemic heart disease patients who died from 1935-1944 were found to have significantly more severe coronary atherosclerotic blockage than those who died from 1945-1955. Also, there was a suggestion that coronary artery clots among patients in the 40-49 and 50-59 year age groups were less prevalent in 1935-1944 than in 1945-1955.

2. When the coronary arteries of ischemic heart disease patients were compared with those of a control group of accident and cancer patients, the former were found to have significantly more severe coronary atherosclerotic blockage and more coronary clots.

3. There was no difference in the severity of coronary atherosclerotic blockage among hypertensive and nonhypertensive ischemic heart disease patients. However, the hypertensive patients developed fewer coronary clots than the nonhypertensive.

4. Body weight at the time of death had no significant relationship to the severity of coronary atherosclerotic blockage among ischemic heart disease patients. However, the body weight did have a strikingly significant relation to coronary clots: 62 per cent of overweight patients had clots; 48 per cent of average-weight patients had clots; and only 27 per cent of underweight patients had clots.

5. Indirect evidence of a possible coagulation defect among ischemic heart disease patients was found. "Extracardiac" clots were found in 34 per cent of these patients, in contrast to 21 per cent of cancer patients. However, ischemic heart disease patients with coronary clots did not have significantly more "extracardiac" clots than those without coronary clots.

6. Data were presented which suggest that ischemic heart disease among diabetic patients differs from ischemic heart disease among the nondiabetic. Ischemic heart disease patients with concomitant diabetes mellitus had significantly more severe coronary atherosclerotic blockage than those without diabetes. On the other hand, only 37 per cent of the diabetics in contrast to 53 per cent of the nondiabetics with ischemic heart disease had coronary artery clots.

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OBSERVATIONS ON SOME POSSIBLE PRECURSORS OF ESSENTIAL HYPERTENSION AND CORONARY ARTERY DISEASE

VII. The Subjective Reaction to the Cold Pressor Test as Expressed in the Verbal Response

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VASOMOTOR hyperreactivity is considered to be one of the earmarks of essential hypertension, but to what extent it precedes the development of hypertension remains uncertain. Of various standardized tests which have been devised to measure the degree of vascular reactivity in a given individual, the cold pressor test of Hines and Brown[1] has been most widely recognized. This test consists of immersing one hand in water at 4° C. for one minute; the resulting rise in arterial blood pressure has been taken as an index of vasomotor reactivity. Although the definition has changed somewhat over the years, Hines[2] and his associates have recently defined hyperreactivity to the cold pressor test as a rise in diastolic pressure of more than 20 mm. Hg, without regard to systolic pressure, and have further stipulated that at some time during the test a diastolic reading of 90 mm. Hg or higher be obtained.[3]

It is known that most patients with essential hypertension are hyperreactors to the cold pressor test,[4,5] and Hines[2] has reported evidence that the cold pressor test may have predictive value in the development of hypertension. He found that 95 per cent of children both of whose parents have established hypertension are hyperreactive to the standard cold pressor test[6]; however, the follow-up of these children to observe the actual development of hypertension in some of them has not been completed as yet. Harlan[7] has briefly reported follow-up studies on 201 healthy young men who had cold pressor tests when they were selected for naval flight training at a mean age of 23.6 years. When they were re-examined 12 and 18 years later, he found that 4.7 per cent of the hyperreactor group had developed hypertension with a diastolic pressure in excess of 100 mm. Hg compared with 1.2 per cent of the normal reactor group. He considered that these findings indicated little correlation between a positive cold pressor test and subsequent hypertension. However, his subjects are still relatively young.

Under the leadership of one of us (C. B. T.), a new approach to identifying the potential victims of hypertension and coronary disease was initiated in 1946 in the form of a long-term prospective investigation of the precursors of hypertension and/or coronary disease. The method consists of making intensive studies of genetic, physiologic, psychologic, and metabolic traits of a large group of healthy young adults who are then to be followed over the years to determine which factors show a positive correlation with the early development of hypertension or coronary disease.[8] The ultimate purpose is to detect those who are highly susceptible in order to protect them by preventive measures.

Vascular hyperreactivity is one of the factors which is being investigated by our group as a possible forerunner of hypertension. In a previous communication,[9] we have shown that three measures of the circulatory response to cold, namely, systolic pressure, diastolic pressure, and heart rate, show approximately normal distribution and behave as continuous variables, giving no convincing evidence of two or more populations, so that any dividing line or cutting point to distinguish hyperreactors from normoreactors is purely arbitrary.

We have noted that the cold pressor test is accompanied by different subjective responses in different subjects. Scattered through the literature on the cold pressor test[10,11] are comments suggesting that the degree of reactivity of blood pressure may be closely associated with the degree of pain experienced by the subject. To determine whether or not this is the case, in the present study we have investigated the relationship between the degree of circulatory reactivity as reflected by the systolic pressure, diastolic pressure, and heart rate and the nature of the subjective reaction as indicated by the verbal response to a standard cold stimulus.

METHOD

All our subjects are Johns Hopkins University medical students. In the present study, 712 subjects in the classes of 1948 to 1959, inclusive, participated. No one gave clinical evidence of hypertension or coronary disease, and no subject was tested who had any significant illness beyond that of a common cold. The cold pressor test was performed by the technique of Hines and Brown[2] as follows:

With the subject stripped to the waist and lying comfortably on a cot, several blood pressure readings were taken until a stable base-line pressure was reached; this usually required from 15 to 30 minutes. Blood pressure was measured in the left arm with the use of a 14 cm. wide cuff and an anaeroid manometer calibrated against a mercury manometer. The point of muffling of the auscultatory sounds was taken as the diastolic pressure. The blood pressure and heart rate recorded just prior to the beginning of the test were taken as the control values. The right hand and wrist were then immersed for 1 minute in water at 4° C., during which time two blood pressure readings were made at approximately 30 seconds and 60 seconds after the hand was immersed. The pulse rate was counted for 15 seconds between the two blood pressure readings. The greatest recorded deviation of the systolic pressure, diastolic pressure, and pulse rate from the control values was taken as the response. Thus the systolic and diastolic changes cited

for a given subject are not necessarily obtained at the same blood pressure reading. Sometimes, during or immediately following the test, a subject spontaneously gave a verbal comment on the sensation induced by the ice water. However, if no comment was forthcoming, the subject was asked, "How did it feel?" and the answer recorded. Leading questions were avoided, and the subjects were not pressed as to further sensations or to elaborate on the expressed sensation.

The verbal responses as recorded on our initial data sheets were classified for coding on IBM cards. The subjective reactions to the cold pressor test as expressed in the verbal responses of our subjects fell into 5 groups which are classified as follows:

1. *Cold* (includes use of the words *cold, cool, chilly, numb,* and mixed responses where *cold* is clearly the dominant sensation expressed).

2. *Pain* (includes *painful, hurts, aches,* and mixed responses where *pain* is clearly the dominant sensation expressed).

3. *Undisturbed* (includes *not bad, nothing much, no special sensation, no pain,* and *not cold*).

4. *Very disturbed* (includes expressions such as *brutal, couldn't stand it, agony, awful, terrible, miserable,* and *thought I was losing my hand*).

5. *Miscellaneous* (includes expressions whose classifications are equivocal and ambiguous such as, *seemed like a long minute, very nervous, wouldn't want to keep it in for two minutes*).

6. Under *none recorded* are included data from students who were given the cold pressor test but for whom no verbal response was recorded. The large majority (86 per cent) of these were in classes of 1952 to 1955.

The subject's age as coded on our IBM cards and as utilized in this study was the age at graduation from medical school. In most cases, the subjects took the cold pressor test during the latter part of the first year of medical school so that the actual age at testing was about 3 years younger than the age recorded on the IBM cards.

In this paper, the term "hyperreactor" has been applied to subjects with a diastolic rise during the cold pressor test equal to or greater than 20 mm. Hg without reference to the absolute level of diastolic pressure attained. This definition is slightly different from the one most recently used in Hines' laboratory.[3]

RESULTS

Of the 935 Johns Hopkins medical students in the classes of 1948 to 1959, there were 712 Caucasian males aged 21 to 31 years who were given the cold pressor test and whose data are the subject of this report. Excluded for the sake of better population homogeneity are 91 females, 22 males of Oriental and Middle Eastern extraction, and 37 white males over the age of 31 years. There remain 73 white males in our files who were noncooperators or who left school before the cold pressor test was scheduled; for these, of course, there are no data to be included.

The mean blood pressure at rest of the 712 subjects immediately before beginning the cold pressor test was 114.0 mm. Hg systolic and 70.2 mm. Hg

diastolic with a control heart rate of 73.4 beats per minute. No one had a diastolic pressure at rest over 100 mm. Hg. The mean increase in diastolic pressure to the standard stimulus was 14.1 mm. Hg, and the systolic increase was 11.5 mm. Hg, with a mean heart rate increase of 4.9 beats per minute. Not all the subjects showed a positive change to the ice water stimulus. During the performance of the cold pressor test, 2.5 per cent showed a decrease in systolic pressure; 1.9 per cent, a decrease in diastolic pressure; and 18.5 per cent, a decrease in heart rate. A diastolic pressure increase equal to or greater than 20 mm. Hg was found in 27.7 per cent of the subjects; these were termed "hyperreactors." Table I shows no significant variation in the control blood pressures and heart rates between subjects of different ages. When the ages from 21 to 26 years and from 27 to 31 years are grouped, the older group always has higher values for each measurement, but the differences are less than 1 per cent. Likewise, Table I shows that, in our population, age as an isolated variable seems to have no influence on blood pressure or heart rate responses to the cold pressor test.

TABLE I. INFLUENCE OF AGE ON CONTROL VALUES AND ON MEAN INCREASES TO THE COLD PRESSOR TEST

POPULATION		CONTROL READING			MEAN INCREASE		
AGE	NO.	SYSTOLIC (MM. Hg)	DIASTOLIC (MM. Hg)	HEART RATE* (BEATS/MIN.)	SYSTOLIC (MM. Hg)	DIASTOLIC (MM. Hg)	HEART RATE† (BEATS/MIN.)
21	4	119.5	72.0	79.5	5.0	7.5	−5.5
22	22	113.2	68.6	69.5	11.2	11.6	7.4
23	59	115.1	69.1	70.6	10.5	13.0	5.3
24	117	114.7	70.5	73.2	11.8	14.1	4.6
25	223	113.8	70.8	73.7	11.6	14.5	4.8
26	121	113.4	69.5	74.0	11.8	15.7	5.8
27	57	111.8	68.9	74.4	12.8	14.3	5.5
28	32	115.8	70.8	73.9	13.0	15.0	3.9
29	33	114.7	70.3	73.9	10.4	9.9	6.5
30	25	116.3	71.3	75.3	11.1	12.6	4.4
31	19	114.2	71.9	71.6	7.6	11.1	1.1
Total	712	114.0	70.2	73.4	11.5	14.1	4.9

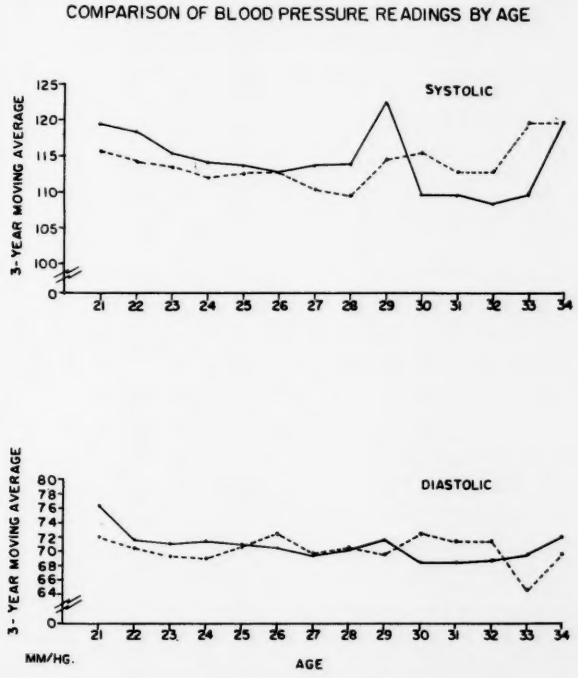
*Eleven subjects had no control heart rate recorded.
†Twenty-eight subjects had no heart rate recorded during the cold pressor test.

The validity of using the age at graduation instead of the age at the time of taking the cold pressor test was examined. From a random sample of 148 subjects within our population, we constructed a graph which plots 3 year moving averages of control blood pressures (Fig. 1). It is noted that the "age at graduation" and "age at test" curves give nearly identical values for about 90 per cent of the sample; therefore, using ages at graduation as originally coded on our IBM cards should not distort our results.

A second important aspect of our data which should be considered before associations with the verbal responses can be meaningfully analyzed is the

relationship between the control values and the changes occasioned by the cold stimulus. Table II indicates a tendency of the blood pressure and heart rate responses to decrease slightly with larger control values. The trend is consistent throughout and suggests a "ceiling effect" (see "Discussion"), which, however, exceeds a 5 per cent level of statistical significance only in the case of the heart rate. A detailed examination of the blood pressure data grouped in Table II broken into steps of 2 mm. Hg has been carried out and reveals no evidence of anything but a unimodal distribution of control blood pressure levels.

The distribution of the various verbal responses to the cold pressor test are shown in Table III. The mean age of the population is 25.5 years with very little difference in mean age between subjects in the five verbal response categories. Responses expressing *cold* and *pain* were of nearly equal frequency. More than one half of the subjects tested expressed either *cold* or *pain* as the most immediate and prominent sensation in response to the cold pressor test. The students voicing *cold* feelings show a mean control blood pressure of 116/71, while those who complained of *pain* have a blood pressure at rest of 114/69. The *undisturbed* and *very disturbed* groups have control blood pressures of 116/68 and 112/72, respectively. There is no significant difference in mean control values for blood pressure or heart rate between the five verbal response groups; in each instance the standard error of the difference between means is less than twice the observed difference.



1.—The control systolic and diastolic pressure readings prior the the cold pressor test plotted as a 3 year moving average. The graph is constructed from a random sample of 148 medical students taken from the present study population. About 90 per cent of the sample is less than 28 years old. The broken line plots age at test and the solid line plots age at graduation on the abscissa.

TABLE II. INFLUENCE OF CONTROL VALUES ON THE MEAN INCREASES TO THE COLD PRESSOR TEST

CONTROL READING	NO.	MEAN INCREASE
Systolic Pressure (mm. Hg)		
<90	4	6.5
90–109	237	12.2
110–129	423	11.6
130–149	47	9.9
150+	1	6.0
Total	712	11.7
Diastolic Pressure (mm. Hg)		
<50	1	4.0
50–59	53	16.2
60–69	293	14.3
70–79	277	13.8
80–89	81	12.0
90–99	7	5.7
Total	712	13.9
Heart Rate (beats/min.)		
40–59	48	6.2
60–79	455	5.8
80–99	175	2.8
100–119	6	4.0
Total	684	5.1

The subjects who expressed *pain* and *very disturbed* feelings had a somewhat greater blood pressure increase to the ice water stimulus than those giving *cold* and *undisturbed* responses. The largest differences were found between the mean diastolic pressure changes where the *pain* group showed a 17.3 mm. Hg increase and the *very disturbed* group a 20.8 mm. Hg increase, as contrasted with increases of 14.4 mm. Hg and 11.7 mm. Hg for the *cold* and *undisturbed* groups, respectively. The difference in diastolic increase of 2.9 mm. Hg between the *cold* and *pain* groups is nearly three times its standard error while the *very disturbed* and *undisturbed* groups have an observed difference of 9.1 mm. Hg which is four times the standard error. Thus, between groups expressing *cold* and *pain* there is a small but significant difference in the magnitude of diastolic pressure increase to the cold stimulus, the *pain* response being associated with the greater increase. The ceiling values were calculated by adding the control value to the corresponding change for each verbal response group and are shown in Table III. Although the mean responses to ice water immersion were somewhat greater for the *pain* than for the *cold* group, the mean control values for the *pain* group were a little lower, so that actually the ceiling values were very nearly the same.

Expressions of marked disturbance (*very disturbed*) to the ice water, as compared to expressions of minimal disturbance (*undisturbed*), are associated with larger diastolic pressure increases which are statistically significant at the 1 per

TABLE III. ASSOCIATION OF VERBAL RESPONSE WITH AGE, CONTROL VALUES, MEAN INCREASES, AND CEILING VALUES FOR THE COLD PRESSOR TEST

	VERBAL RESPONSE						TOTAL
	COLD	PAIN	UNDISTURBED	VERY DISTURBED	MISC.	NONE RECORDED	
Total No.	193	197	50	13	30	229	712
No. hyperreactors	52	83	7	9	5	40	196
Mean age (years)	25.3	25.8	25.5	24.6	25.3	25.6	25.5
Control							
Systolic (mm. Hg)	115.9	113.6	115.9	111.8	115.5	112.3	114.0
Diastolic (mm. Hg)	70.9	69.0	68.3	72.2	72.8	70.6	70.2
Heart rate* (beats/min.)	73.2	73.9	72.4	72.6	74.5	73.4	73.4
Increase							
Systolic (mm. Hg)	11.8	13.9	8.8	13.0	12.1	10.0	11.6
Diastolic (mm. Hg)	14.4[a]	17.3[a]	11.7[b,c]	20.8[b,d]	14.2	11.5	14.2[c,d]
Heart rate† (beats/min.)	5.1	6.1	4.9	7.9	7.2	4.3	5.0
Ceiling							
Systolic (mm. Hg)	127.7	127.5	124.7	124.8	127.6	122.3	125.6
Diastolic (mm. Hg)	85.3	86.3	80.0	93.0	87.0	82.1	84.4
Heart rate† (beats/min.)	78.3	80.0	77.3	80.5	81.7	77.7	78.4

Comparisons a,b,c, and d indicate the significant differences in response to cold (see text).
*Eleven subjects had no control heart rate recorded.
†Twenty-eight subjects had no heart rate recorded during the cold pressor test.

cent level. These latter groups are relatively small. When the diastolic responses in the *undisturbed* and *very disturbed* groups are compared with the total population of 712 subjects, the observed differences are greater than two times and three times their standard errors. Thus, the mean diastolic increase of the *undisturbed* group is *smaller* than that of the total population, and the mean diastolic increase of the *very disturbed* group is *larger* than that of the total population. Fig. 2 illustrates the difference in mean percentage increase of blood pressure and heart rate to cold immersion between the verbal response groups.

We have examined each verbal response group as to the proportion of hyperreactors (diastolic pressure increase equal to or greater than 20 mm. Hg). On the basis of the expected verbal responses, using the distribution from Table III for comparison by a chi-square test, we find significantly ($p = 0.001$) more hyperreactors in the *pain* and *very disturbed* groups than in the population as a whole. The *pain* category is made up of 42.1 per cent hyperreactors and the *very disturbed* group 69.2 per cent, in contrast to 27.7 per cent hyperreactors in the total population.

With regard to the systolic blood pressure and heart rate increases following the cold stimulus, in no case do differences between the verbal response groups in Table III reach an important magnitude or high level of statistical significance.

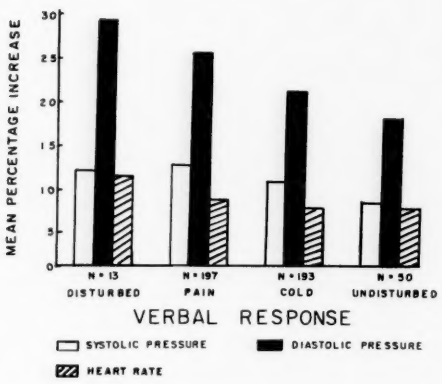


Fig. 2.—Mean percentage increases $\left(\frac{\text{mean increase}}{\text{mean control value}} \times 100\right)$ in systolic pressure, diastolic pressure, and heart rate. These percentage increases to the cold pressor test are shown for each verbal response group.

There is a small but consistent tendency toward higher mean systolic blood pressure readings and heart rates in the *pain* and *very disturbed* groups than in the *cold* and *undisturbed* groups. Here also the ceiling effect tends to minimize the small differences in systolic blood pressure response between verbal response groups but does not appear to affect the heart rate responses.

DISCUSSION

Although we find that the mean diastolic increase during the cold pressor test is statistically greater in subjects who, as a combined group, give *pain* or *very disturbed* responses than in those who verbalize *cold* or *undisturbed* feelings, the absolute mean difference is relatively small (< 4 mm. Hg). A larger proportion of hyperreactors is found in a combined *pain* and *very disturbed* group (43.8 per cent) than in the total population (27.7 per cent). The hazard of linking too closely the pain response with the phenomenon of hyperreactivity, however, is clarified by observing that less than one half of the hyperreactors may be expected to express *pain* or *very disturbed* feelings.

Other studies are in agreement with our findings. Glaser and Whittow[12] carried out repeated immersions similar to the cold pressor technique we use and arrived at little correlation between circulatory response and pain sensation. In a Canadian study[13] immersion of a limb in cold water produced a greater rise in blood pressure in Eskimos than in Caucasians from the more temperate parts of Canada although the subjective responses of Eskimos to cold were less marked than those of other Canadians. As part of an inquiry into the physiology of the cold pressor reaction, Whittow[14] determined that subjects could distinguish subjectively between cold water at 1° C. and 6° C. but not between water at 2° C. and 6° C.; however, immersion of the hand in water at 2° C. caused significantly greater pressor responses than did immersion at 6° C. It appears that a change in

the cold pressor response may occur without a concurrent change in the subjective assessment of pain.

On the other hand, Reid and Teel,[10] as a result of their experience with the cold pressor test, stated that the rise in blood pressure is due to the pain induced by the ice water. Wolf and Hardy[11] found direct correlation between the degree of cooling, the intensity of pain induced by the cold, and the height to which the blood pressure rose. They considered 18° C. to be the critical temperature below which pain occurs, with the intensity of aching, continuous, nonpulsatile pain progressing linearly with decreasing temperatures down to −2° C., always reaching its maximum at about 1 minute. Between 10 and 60 seconds after immersion in cold water and approximately coincident with the onset of pain, a sharp rise in blood pressure is said to have occurred, reaching its maximum at about the point of maximum pain. If the hand was then left in cold water, the pain subsided in 4 to 5 minutes, at which time the blood pressure had returned to "normal."

It is of interest that the subjective sensation produced by the cold pressor test exhibits a lack of spatial summation. Immersing one finger at 0° C. causes pain equal in intensity to that experienced when the whole hand is immersed.[11] Whittow[14] makes the observation that it seems to make no difference in the blood pressure response to cold whether the whole forearm or just the fingers are immersed.

Wolf and Hardy[11] stated that aspirin, codeine, and alcohol lower the pressor effect because they reduce pain; however, barbiturates, which in sedative doses have little effect on the pain threshold, also are said to reduce greatly the blood pressure response to a cold stimulus.[10] This suggests that the pressor response is not simply associated with the subject's appreciation of pain.

The fact that we find no significant change in blood pressure with age in our population may be accounted for by the comparatively narrow age range of eleven years, with the large majority of subjects closely grouped in the early twenties. Comstock[15] raises the question that the blood pressure increase in a large population may not be due to a gradual increase which is inherent in aging, but rather to a sudden shift of a limited number of subjects from normal to a hypertensive blood pressure range. His data reveal that the frequency distributions of blood pressures shift toward higher levels with advancing age, with a small increase in mean diastolic pressure and no increase in mean systolic pressure during the second and third decades. Master[16] shows a more consistent increase in blood pressure from the age of 16 to 64 years.

In our study we find no change in the cold pressor response with age; however, Russek and Zohman,[17] working with a broader age range, have evidence to show a rising incidence of hyperreaction with succeeding decades. They conclude that age exerts an important influence on the response to the cold pressor test. Whether or not the increasing prevalence of hyperreaction with age is due to an increase in response peculiar to aging or, more simply, to an increasing number of hypertensive individuals in the population cannot be decided at this time. It has been pointed out that essential hypertension often is accompanied by hyperreaction to the cold pressor test.

In contrast to the circulatory hyperreactivity to a cold stimulus which is seen in relation to the elevated resting blood pressure of patients with essential hypertension[2,18,19] there is evidence[20] that in "normal" subjects the response to the cold pressor test is actually lessened when the blood pressure is first raised by epinephrine or ephedrine or by means of the pressor reflex from muscle. In our population of normal young men, we detected a slight tendency of the pressor response to fall off with higher values of resting blood pressure and heart rate. These observations may support Hines' concept of a "ceiling" for the cold stimulus which is characteristic for the individual and which dictates a reduced response when a basal blood pressure is not used to calculate the pressor change.[5] Another paper from the same laboratory[21] also draws attention to the importance of first obtaining a true basal blood pressure reading in order to obtain full and consistent responses to a cold immersion stimulus. Previously, we have noted a similar "ceiling effect" in studying the circulatory response of healthy young men to smoking[22]; responses were more marked in an early morning fasting state (basal conditions) than before lunch (resting conditions).

In the present study, we have not attempted to evaluate the contributions made by increased vasoconstriction and by increased cardiac output to the overall pressor effect. The fact that an acceleration in heart rate during cold immersion was observed in a large majority of subjects strongly suggests that a change in peripheral resistance is not the only factor of importance, and our previously reported observation that cardiac output, as measured on the ballistocardiograph, may increase sharply during the test supports the view that cardiac participation often occurs.[23]

CONCLUSION

We conclude that in healthy young adults there is an association between subjective reaction and the magnitude of the pressor response to cold. However, the relationship is not striking, and there are many individual exceptions to the generalization that expressions of pain and marked disturbance are associated with larger blood pressure and heart rate responses. Our data would certainly not support the hypothesis of a direct cause-and-effect relationship between the subjective reaction and the pressor response to a standard cold stimulus. It would be hazardous to attempt to separate individuals who have vasomotor "hyperreactivity" from those with "normoreactivity" on the basis of the verbal response to the cold pressor test. Only time and the careful follow-up of our subjects will tell us if the cold pressor test is adequate to select with useful precision those young adults who are most likely to develop the sustained vasomotor tone of essential hypertension.

SUMMARY

1. The study population consisted of 712 white male medical students who took a standardized cold pressor test.

2. The relationship between the degree of circulatory reactivity and the character of the subjective verbal response to an ice water stimulus has been investigated.

3. Verbal response groups expressing *pain* and *very disturbed* feelings have somewhat greater mean blood pressure and heart rate increases to a standard cold stimulus than groups who indicate *cold* or minor *undisturbing* sensations. The differences, although statistically significant, are never large, and when the ceiling effect is taken into account most of these small differences between verbal response groups are minimized.

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PSEUDOMYXOMA PERITONEI DUE TO MUCOCELE OF THE APPENDIX

A Report of Four Cases and Review of the Literature

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PSEUDOMYXOMA peritonei secondary to mucocele of the appendix, a condition considered to occur rather infrequently, has been found in a 525 bed general hospital 4 times in the interval from 1948 to 1956. Pizzi[1] noted one case of pseudomyxoma peritonei in 2,300 appendectomies. Timoney[2] observed one case in 3,087 appendectomies and Woodruff and McDonald[3] reported only 4 cases in 43,000 appendectomies performed at the Mayo Clinic up through 1940. Weaver[4] found only one case of pseudomyxoma peritonei in 6,223 appendectomy specimens.

The records of Queens General Hospital, Bellevue Hospital, and the Brooklyn Veterans Administration Hospital were surveyed from 1948 through 1956, and not one instance of the disease was recorded. Up to 1945, this disease had been reported only 90 times in the literature.[5] Subsequent to this, we have found another 16 cases reported.[1,10-14,16,21-23] Thus, the finding of 4 cases at Maimonides Hospital, where approximately 3,200 appendectomies were performed during the period in question, constitutes a surprising incidence of this condition.

Pseudomyxoma peritonei was first described by Pean[6] in 1871 and until 1910, when the first case was recorded in a male,[7] it was felt to be exclusively associated with ovarian tumors.

Subsequent reports have illustrated that pseudomyxoma peritonei may arise from vestigial urachal cysts,[8] mucoid-secreting carcinomas of the gastrointestinal tract,[9] and numerous other intra-abdominal structures.[23]

Because of the relatively few reports concerning this syndrome when it is of appendiceal origin, the following 4 cases seen as Maimonides Hospital are presented.

CASE REPORTS

Case 1.—J. B., a 64-year-old white man, was admitted to the hospital on July, 1948, with a history of crampy, lower abdominal pain for one day. There were no chills, fever, or change in

bowel habits. After admission, the patient developed fever, up to 105°F., with chills. Tenderness and spasm were noted in the right lower quadrant. Because of persistent fever and abdominal pain, the tentative diagnosis of appendiceal abscess was made and operation undertaken. No free fluid was found in the peritoneal cavity. A mass, which contained seropurulent material, was found lateral to the cecum. Drainage was performed and the abscess cavity left in situ. The postoperative course was unremarkable. The patient, who had been asymptomatic after discharge, re-entered the hospital six months later for an interval appendectomy. The appendix was noted by the surgeon to be bound down by adhesions, thickened and scarred.

The pathologic specimen consisted of an appendix measuring 6 cm. in length. The central portion was distended and its diameter measured up to 1.3 cm. The serosal surface was covered with bands of connective tissue. Several small cystic spaces, measuring up to 0.3 cm. in diameter, containing clear mucoid material, were present 1 cm. proximal from the line of resection. The distal third of the serosal surface was intimately adherent to the fat tissue and contained cystic spaces filled with gelatinous fluid. The lumen of the distal third was patent but eccentric. The distended portion contained clear gelatinous material. In the proximal third, a connection between the lumen and cystic mass was present.

Between the portion of the appendix contained within the cystic mass and the distal third, a small portion of the lumen appeared to be occluded, and 0.5 cm. from the proximally resected end the lumen also appeared to be occluded. Microscopic sections showed the proximal and distal portions of the appendix to be obliterated. Sections of the mid-third revealed dilation of the lumen with flattening of the mucosa and fibrosis and chronic inflammation of the wall. The lumen communicated through a defect in the wall with a large accumulation of mucus in the mesenteric fat and on the serosal surface. Foreign body granulomas were also noted.

The diagnosis was perforated mucocele of the appendix with pseudomyxoma peritonei. The postoperative course was not remarkable and long-term follow-up reveals that the patient has enjoyed good health up to the present time.

Case 2.—G. M., a 60-year-old white woman, entered the hospital on April 1, 1951, complaining of crampy lower abdominal pain, diarrhea, and anorexia for 4 weeks. There was no history of melena or mucus in the stools or of genitourinary difficulty. On physical examination, a cystic, globular mass was noted to ascend out of the pelvis and extend upward and to the right of the umbilicus. The mass was not tender and no other organs or masses were palpable. Pelvic examination revealed a cystic, slightly movable mass in the right fornix and suprapubic area. There was also a fullness in the left fornix. Laboratory findings were not contributory. Barium enema revealed filling through the entire colon and displacement of the mesial border of the cecum upward. No filling defects were noted. The ileum was noted to ride high, as if across a lower abdominal tumefaction about the size of a 6 months' pregnancy. No differential densities could be seen. The preoperative diagnosis was ovarian cyst.

Laparotomy revealed a thickened hemorrhagic peritoneum. About 500 c.c. of pseudomucinous material was found. This adhered to the peritoneum, pelvic organs, and intestines. In the region of the appendix, a fist-sized mass was noted. The mass and the appendix were removed.

Pathologic studies were consistent with pseudomyxoma peritonei associated with mucocele of the appendix.

The postoperative course was unremarkable. The patient was well for about 2 years, when she developed recurrence of abdominal pain with vomiting and enlargement of the abdomen.

Physical examination revealed multiple nontender masses in the abdomen. Smaller masses were noted on rectal and pelvic examination. Laparotomy disclosed 250 c.c. of straw-colored material. The greater omentum was studded with numerous nodules, some of which contained gelatinous material. Similar nodules were noted on all viscera. Pathologic sections revealed nests of mucus-forming cells and islands in a dense connective tissue stroma. These findings were felt to be compatible with pseudomyxoma peritonei.

Postoperatively, the patient suffered a cerebral vascular accident and died. No postmortem examination was performed.

Case 3.—R. C., a 57-year-old white woman, entered the hospital for the first time in September, 1948, with a chief complaint of dull, aching, intermittent pain in the lower abdomen, of about one and a half years' duration. There were no complaints associated with the gastro-

intestinal or genitourinary systems. Six days prior to admission, the pain had become more severe and persistent. Physical examination was negative, with no tenderness or palpable abdominal masses. Laparotomy revealed a large mass surrounding the appendix, adherent to and involving a loop of ileum and a portion of the sigmoid colon. There was compression of the lumen of the bowel by this mass. Lymph nodes and liver were free of involvement. Resection of ileum, cecum, and ascending colon was accomplished and ileotransverse colostromy performed. Pathologic study revealed numerous clusters of grapelike structures which on section were shown to consist of locules filled with a mucoid material. The epithelium of the locules was noted to range from cuboidal to columnar. Considerable granulation tissue was noted and in various areas, foreign body granulomas. The appendix presented a mucocele in its distal portion and on microscopic section was noted to have a hyaline wall with marked loss of epithelium. The patient was asymptomatic until September, 1951, when she was readmitted with abdominal pain and an incisional hernia which had been present for a month. The hernia was corrected and specimens of peritoneum and omentum revealed recurrent pseudomyxoma. Five months later, the patient was readmitted with marked abdominal swelling and a fluid wave, complaining of heaviness in the abdomen and loss of appetite. Omentectomy was performed and a large quantity of fluid removed. The entire cavity was noted to be studded with tumors. The patient was discharged and, unfortunately, lost to follow-up.

Case 4.—W. A., a 62-year-old white man, was admitted to the hospital for the first time on April 1, 1958, with the chief complaint of increasing girth of the abdomen and a weight loss of 23 pounds in the year prior to admission. He had dieted voluntarily, but noted that the abdomen had continued to grow in size despite weight loss. There was moderate increase in fatigability and some anorexia. He denied any change in bowel habits, melena, alcoholic intake, or history of jaundice. Similarly, cardiovascular-renal history was normal. Physical examination revealed a well-developed, poorly nourished white male. Pertinent findings were limited to the abdomen, which was noted to be markedly distended, with protrusion of the umbilicus. A fluid wave and shifting dullness were elicited. Palpation revealed a series of irregular masses particularly in the left half of the abdomen. Rectal examination was notable in that a firm "shelf" was palpated. Abdominal paracentesis was performed and about 20 c.c. of a "consommé-jelly" type of fluid was obtained. Pathologic study of this fluid revealed neither mucin nor tumor cells. Laparotomy was undertaken and peritoneal biopsy performed. A large mass with a volume of 2 gallons was noted. Suspended within this mass were numerous particles of round and flat shape. The mass was of thick jellylike consistency. Thickening of omentum and peritoneum was observed and at the inferior border of the stomach, an infiltration was noted, which was felt to be the primary site of the suspected malignancy.

The pathology report revealed findings of pseudomyxoma peritonei.

Re-exploration of the abdomen for appendectomy was performed one week after the initial procedure and considerable scarring and adhesions were noted in the right lower quadrant. The appendix was found to be distended and thin walled. Microscopic study of the appendix revealed a markedly hyperplastic mucosa with papillary folds. Large goblet cells of the colonic type were noted. The glands were noted to rest on a fibrotic, sparsely cellular submucosa. Fibrous obliteration of the tip of the appendix and chronic inflammatory changes of the wall and periappendiceal tissues were noted. The findings were felt to be compatible with pseudomyxoma peritonei.

The patient was discharged and did relatively well for about one and a half years, but then noticed slowly increasing abdominal girth. He was readmitted in August of 1958. Repeat studies were performed and the patient was discharged without any specific therapy. His third admission occurred in October, 1959, and was prompted by increased difficulty in ambulation. The patient stated that he had had x-ray therapy to the abdomen after discharge, but that the abdomen had continued to expand.

Exploratory operation was performed and the abdomen was noted to contain multiloculated cavities filled with gelled material. The loculations varied in size from 3 cm. to one which filled about 50 per cent of the celomic cavity. Drainage of many of the cavities was performed and Foley catheters were placed in the abdomen. Postoperatively, the patient felt considerably improved. He was discharged with the catheters in situ and returned 4 weeks later because of increasing toxicity.

Re-exploration of the abdomen showed the peritoneal fluid to be infected and cultures revealed gram-negative enteric organisms. Postoperatively he developed numerous complications and died.

Postmortem examination was obtained and confirmed the diagnosis of pseudomyxoma peritonei.

It is of interest that the original operative suspicion of a primary neoplasm of the stomach was not confirmed.

DISCUSSION

The diagnosis of pseudomyxoma peritonei of appendiceal origin is rarely made on the basis of clinical or laboratory information. Sometimes, even abdominal paracentesis does not reveal the diagnosis and only at surgical exploration is the true nature of the lesion elicited. Brennan[10] reported the cases of 2 patients with essentially the same symptoms and was able to suggest the diagnosis preoperatively in the second case.

If the entity is thought of, then the history may be suggestive, although by no means diagnostic. First, the possibility must be considered when the patient presents himself with the complaint of increasing abdominal girth and little else in the way of systemic manifestations. Disorders such as malignancy, congestive heart failure, and cirrhosis of the liver more often produce signs of debilitation by the time that the patient presents with an enormous abdomen. Also, the relative longevity of the patient with pseudomyxomatous ascites is in sharp contrast to the life span found in the other clinical conditions. A long history of pain typical or atypical of appendicitis should alert one to consider mucocele of the appendix and possibly pseudomyxoma.[12] However, only 2 of our patients (Cases 2 and 3) presented complaints of abdominal pain. Edlund[12] ascribed this pain to intermittent bouts of intestinal obstruction. Urinary frequency has also been noted to occur. This is presumably due to pelvic involvement. However, none of the patients had complaints referable to the urinary tract. Syncopal episodes, apparently due to hypoglycemia, have also been recorded as a presenting complaint.[16] These were not elicited in our patients.

The findings at physical examination will depend largely on the stage of the illness during which the patient is examined. Characteristically, one sees a patient with a striking disproportion between the chest and huge abdomen, the so-called "jelly-belly."[5] Fig. 1 shows the last patient (Case 4) and was taken at a time when his only complaint was that the abdomen was uncomfortably distended. Abdominal examination is said to be helpful, if one perceives a fluid wave without shifting dullness.[10,11] In this case, however, both shifting dullness and a fluid wave were thought to be present by all observers, in spite of the fact that the material aspirated was thick and tenacious. If the distention is not extraordinary, a mass is usually palpated.[10,11,12] This mass may be due to the original mucocele or may be one of the many new growths of pseudomyxoma within the peritoneum. There is little to distinguish these masses from other new growths. Masses were palpable at some time in the course of Cases 2, 3, and 4. Rectal or pelvic examination may also reveal the presence of a mass (as noted in Cases 2 and 4). Pseudomyxoma on occasion has presented as an inguinal hernia.[13,22,23]

Fig. 1.—Case 4.

Radiologic study may reveal an incompletely calcified ring in the right iliac fossa[5] or multiple radiopaque densities of varying size that are more dense peripherally than centrally.[16] These findings, however, are not specific for pseudomyxoma of appendiceal origin. Similar findings have been demonstrated in the syndrome secondary to urachal cyst,[8] as well as in other calcifying cysts of the celomic cavity.[15] In none of our cases were these radiographic alterations noted.

Laboratory tests are usually not rewarding diagnostically, although it has been rarely noted that pseudomyxoma may be associated with hypoglycemia and a slow rise in blood sugar, following oral administration of glucose.[16] In none of our patients was a low blood sugar level seen.

As observed earlier, the diagnosis is usually unsuspected and made on paracentesis or exploratory laparotomy. It is of interest that in Case 4, even at laparotomy, the diagnosis was not made because there were findings that pointed to the stomach as the site of primary malignant disease. Peritoneoscopy may be a helpful technique in elucidating the diagnosis.[14]

A number of investigations have attempted to evolve the pathogenesis of pseudomyxoma peritonei of appendiceal origin. It should be observed that the term pseudomyxoma is actually a misnomer, since pseudomucin has been shown to be mucin which has lost its characteristic alcohol coagulability as a result of aging.[17]

The development of an appendiceal mucocele is considered to be fundamental to the genesis of this entity.[7,18-21] The mucocele, in man, is thought to develop following obstruction of the lumen of the appendix with continued production of mucus distal to this obstruction.[18,19,20] Mucoceles have been induced experi-

mentally in the rabbit by ligation of the cecal appendage without compromising the vascular supply.[18,19,20]

It is postulated that, because of the thicker muscular coat of the human appendix, a longer induction period may be required to produce a mucocele than in the rabbit cecum.

Rupture of the mucocele with evacuation of the contents into the peritoneal cavity appears to be the next step.[18,19] Some authors contend that initiation and progression of the generalized myxomatous state depends on the transfer of viable epithelial cells into the peritoneal cavity where these cells may become implanted and continue to produce mucin.[3,7,16,18] There is another school of the opinion that the extruded mucus acts as an irritant, causing a foreign body type of reaction. Metaplasia of the mesothelium of the peritoneum first to cuboidal and then to columnar and glandular epithelium follows. It is this metaplastic tissue which then produces the excessive mucin.[19,20,21] Cheng[20] observed initially successful "takes" of transplanted appendiceal epithelium. However, there was no mucin production and walling off of the "take" was inevitable. The possibility has been raised that the obstructing process was not carried out long enough in the experimental animal to convert it to the point where the appendiceal epithelium would sustain itself on transplantation.[22] On the other hand, Cheng was able to induce a state remarkably similar to the generalized pseudomyxoma of man by transplanting nonviable, chloroform-treated mucocele contents from one rabbit to another. This would seem to favor the concept that the mucin is produced by an irritative phenomenon.

Cheng[20] and Carleton[21] are of the opinion that a fistula must be established and maintained in order that a generalized pseudomyxomatous condition evolve. They suggest that ablation of this tract will result in regression of the illness. In only one of our cases was such a conduit found (Case 1). Ablation of the entire appendix (and hence of any fistula present) has been noted only occasionally to result in amelioration of the pseudomyxomatous state, as illustrated by Case 1. Cases 2 and 4 certainly received no permanent benefit from appendectomy and tract removal. We do not deny the possibility that the tract may be required for a period of time, after which its presence is no longer necessary and the process may then be self-perpetuating. This would account for the many cases without improvement after the mucocele has been removed.

The classification of the mucocele has been a further source of disagreement.[3,13,16,21,22] Histologically, Woodruff and McDonald[3] divided mucoceles into so-called benign cysts and a smaller group of adenocarcinoma in situ. They contended that pseudomyxoma peritonei was consequent only upon the development of the malignant variety. Transition from the benign to the malignant form was suggested. Carleton,[21] in a detailed histologic study, was able to demonstrate a sequence that appeared to be related to the chronicity of the obstruction of the lumen. Following obstruction, glandular dilation was first noted. This was followed by formation of papillae and finally atrophy of the epithelium. Carleton feels that the papillary phase of the obstructed mucocele corresponds to the malignant mucocele described by Woodruff and McDonald. Only one of our

patients was noted to show papillary changes (Case 4) and here no other signs of malignancy were observed.

Therapeutic measures in this illness are extremely difficult to evaluate, primarily because of the relative infrequency of the syndrome and the capricious course of pseudomyxoma. Cases are recorded where the patient has been seen early in the course of the illness, and appendectomy was performed, only to be followed by an inexorable progression, terminating in intestinal obstruction and death. Other patients with the full-blown picture are noted to live for many years, requiring only palliative paracentesis. On occasion, these patients may even show spontaneous resolution of disease.[23] In the light of this fact, the difficulty in evaluating the efficacy of appendectomy, x-ray therapy, and intraperitoneal instillation of radioisotopes or enzymes must be appreciated.

Early appendectomy[11,12,18] would appear reasonable if one accepts the concept of a foreign body peritonitis that requires a certain "level of activation" and then becomes self-perpetuating. Certainly, if the fistula concept is valid, removal of the appendix is justified.[21] Once the process is established, and the appendectomy is performed, multiple paracentesis may be helpful in keeping the patient comfortable and relatively active.[11,24] Intraperitoneal instillation of the proteolytic or mucolytic enzymes[10,11,23] has been reported to aid in the evacuation of the fluid, although the dangers of fistula formation, particularly with trypsin, are quite definite.[23] Radiotherapy by direct isotope instillation or external radiation has been reported to result occasionally in regression of the process.[5,10-12,23] However, a number of cases have been presented in which the radiation therapy was ineffective.[13,23] Case 4 had radiotherapy, but nevertheless showed a progressively deteriorating course. No reports regarding intraperitoneal use of alkylating agents were found in the survey of the literature.

SUMMARY

1. Four cases of pseudomyxoma peritonei secondary to ruptured mucocele of the appendix are presented. An important diagnostic clue is the presence of increasing abdominal girth, without symptoms of severe constitutional illness. The prolonged course furthermore is unusual in malignancy, or in cardiac or hepatic disorders.

2. The etiology and pathogenesis of this disorder are discussed. The importance of the obstructed appendix with secondary mucocele formation and subsequent rupture and development of pseudomyxoma peritonei in both the experimental animal and in the human is discussed.

3. Therapy at present is largely unsatisfactory and primarily directed toward the removal of whatever quantities of mucin can be mobilized by means of paracentesis or operation.

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Book Reviews

RESPIRATION, PHYSIOLOGICAL PRINCIPLES, AND THEIR CLINICAL APPLICATIONS. By P. H. Rossier, A. A. Buhlmann and K. Wiesinger. First English Edition. Translated from second German edition by Peter Luchsinger and Kenneth Moser. St. Louis, 1960, The C. V. Mosby Company. Pp. 505, indexed. Price $15.75.

During the last fifteen years, there has been a tremendous increase in our knowledge of human pulmonary physiology. New methods of study have resulted in better understanding of distribution of air and blood to the lungs, the oxygen diffusing capacity, cardiac output, pulmonary arterial pressure, mechanical characteristics of the chest wall, and the work of breathing.

There have been several attempts to interpret pulmonary function tests for the clinician. Systems for the comprehensive investigation of pulmonary function have been presented in monograph form. *Respiration, Physiological Principles, and Their Clinical Applications* is unique in that it attempts to survey, compare, and criticize the methods used by different investigators to study various aspects of pulmonary function. There are four sections—one on the physiology of respiration, a second on investigative methods, a third on the pathophysiology of respiration, and the last on pulmonary insufficiency in clinical practice.

Dr. P. H. Rossier of Zurich has been primarily interested in pulmonary pathophysiology for over thirty years. This book is a translation of the second edition of his book. The translators have attempted to broaden the coverage of the book by including concepts and methods developed in the United States. The authors have succeeded in presenting a comprehensive survey of human pulmonary physiology and pathophysiology. There is an eighty-page bibliography arranged by topics.

On page 95 the statement is made that Cournand suggested that systemic arterial hypoxemia is the cause of the pressure rise in the pulmonary circulation. Actually in patients with pulmonary emphysema, Cournand noted a correlation between arterial hypoxemia and pulmonary arterial pressure. His view is, however, that hypoxemia is related to the disturbance in ventilation/perfusion relationships and that local hypoxia causes an increase in pulmonary capillary resistance.

There are three groups of physicians who should find this book helpful. Medical students interested in delving into the mysteries of pulmonary physiology will find it authoritative and comprehensive. Pulmonary physiologists will be able to find many basic articles summarized and methods compared. Clinicians interested in interpreting pulmonary tests will find forty-eight examples of the application of such tests in different clinical conditions. These cases are well selected and illustrate the practical value of pulmonary tests in clinical medicine.

Douglas Carroll

EVALUATION OF DRUG THERAPY. Proceedings of the Symposium on Evaluation of Drug Therapy in Neurologic and Sensory Diseases held at the University of Wisconsin, May, 1960. Edited by Francis M. Forster, M.D. Madison, Wisconsin, 1960, University of Wisconsin Press. Pp. 167, indexed. Price $4.00.

The pertinent title here is actually the subtitle, since this slim book records only some brief talks by representatives from the fields of pharmacology, the drug industry, biostatistics, and the Food and Drug Administration, followed by the panel reports of some work groups concerned with evaluation of therapy of various sorts in epilepsy, vertigo, neuralgias, headache, multiple sclerosis, myopathies, and Parkinsonism.

The sections on planning of clinical trials are perfectly sound and sensible, but are also (intentionally, one would assume) fairly elementary. (An exception is Shirley Ferebee's provocative discussion of "controls in search of a study.") The panel reports constitute the unique portion of the book, but unfortunately they vary tremendously in quality, and only a few will be of any great help to future planners of clinical trials in neurology. The glaucoma report, in fact, is just plain badly written, with its ". . . animal experimentation which involved not only animals, but . . . human volunteers," remedies with "glaucoma properties," EEG records for evaluating therapy (!), etc.

The meeting—allegedly only the first in a series—unquestionably was a useful one for its participants, and it is to be hoped that they continue their pharmacologic toil in the neurological vineyard. (Of considerable interest, for example, is the willingness of the conferees to agree on the paucity of unassailable data on the clinical efficacy of "standard" drugs for many neurological diseases.) At the same time, one wonders whether anything more than cheap soft-cover reports of meetings such as these is really warranted.

Louis Lasagna

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AGING . . . SOME SOCIAL AND BIOLOGICAL ASPECTS. Symposia Presented at the Chicago Meeting of the American Association for the Advancement of Science, December 29-30, 1959. Edited by Nathan W. Shock. Washington, D.C., 1960, American Association for the Advancement of Science. Pp. 427. Price $8.50. ($7.50 to AAAS members.)

Five major areas of aging are explored in this book: (1) implications for society, (2) aging in tissues and cells, (3) aging in the total organism, (4) theories of aging, and (5) oral aspects of aging.

Four to five papers are presented in each division by some of the country's outstanding contributors to the field of aging. The aim of these symposia was, as the editors state, to "place primary emphasis on the development of ideas rather than on detailed reviews of the literature." The important contribution of this volume is that it pinpoints problem areas, thereby planning the development of future research on aging. Consequently, the symposia raised more questions than they answered. As far as social aspects are concerned, in this reviewer's opinion the article by John W. McConnell, "Economic Aspects," is the key article in the entire book. If research in the areas which he discusses can be developed, and some solutions to the economic problems of the aging population can be solved, a great many of the social, emotional, and medical problems will be greatly ameliorated.

After reading this book, one might have the impression that a separate specialty in clinical medicine is needed, i.e., Geriatrics. There certainly is no question that the problems the geriatric patient presents are sometimes quite unusual and certainly often very complex, but I think it is a mistake to develop a new specialty for the aged patient. I think it better to enlarge the program in internal medicine so that the internist can be exposed to the new thinking concerning the clinical aspects of the aging patient.

To anyone who has been working in the field of geriatrics for any period of time, nothing in this volume will be new. However, it is a very neat package of almost all problems related to aging, and it makes an excellent reference book for those now working with geriatric patients, as well as a very good introduction to those who are becoming interested in this field. One important subject, however, was not discussed in this book. It is a subject which, in my opinion, should have been included as a major topic, i.e., "over-all coordination of services to the aged." This is a prime area where study is needed if the results of clinical research are ever to be applied efficiently. Such coordination of services would also have a profoundly healthy effect on making available research material in larger quantity with better follow-up. We should provide a well-organized service program into which we build research, rather than develop many fragmented research projects from which we hope some service will come.

Much to my relief, the words "senior citizen" were not used once in this volume.

Mason Faulconer Lord

MEDICAL AND BIOLOGICAL RESEARCH IN ISRAEL. Edited by Moshe Prywes. The Hebrew University of Jerusalem and Hadassah, The Women's Zionist Organization of America. Distributed by Grune & Stratton, Inc., New York. Pp. 562, indexed. Price $8.00.

This review by Israeli scientists is an inventory of the progress of research in biology and medicine during the first ten years of their nation. Although faced with many urgent problems that demanded applied research, an early decision was made to foster basic research alongside its more practical counterpart.

The various chapters run a gamut of subjects in varied fields of biology and medicine. The subjects are often introduced by a historical background, sometimes traced to antiquity. The medical subjects are frequently influenced by the genetic and sociologic factors of a recent influx of population. The immigration has varied from the surviving Ashkenazi Jews of Central Europe to the ancient, highly inbred communities of Iraqui Jews. This has afforded opportunities for genetic research in such inherited traits as thalassemia, favism, and periodic disease.

In its whole, this volume presents an impressive panorama of vigorous activity in the establishment of science on a broad base by a new nation. Many valuable contributions have already been made. An insight is afforded into the factors in planning the establishment of educational and research institutions. The reader may be led into drawing an analogy to the many new nations of Africa and Asia. The analogy is a difficult one, for Israel started off with the rudiments of education, science, and trained individuals. The other nations are beginning from a much lower base line. The editors state in the preface: "Our objectives will be well served if others, with problems similar to our own, may benefit from a description of Israel's efforts to apply scientific methods to the solution of its problems."

Albert Schilling

LAENNEC: HIS LIFE AND TIMES. By Roger Kervran, M.D. Translated from the French by D. C. Abrahams-Curiel. New York, 1960, Pergamon Press, Ltd. Pp. 213, not indexed. Price $3.50.

Why can't most medical historians write better? It is true that Laennec's life was perhaps less exciting than might be desired by an aspiring novelist with one eye on movie rights—yet he lived in exciting times and his scientific career and personal life were certainly not without drama and tragedy. Dr. Kervran has, unfortunately, not written a book to be read with enjoyment by most physicians. He has apparently scrutinized all sorts of authentic historical documents and *Laenneciana*, but the resulting book lacks both momentum and cohesion, defects probably not attributable to inadequate translation.

One more complaint: Was it just bad judgment or the ultimate in philological snobbery to reproduce, without translation, verse in *Breton dialect?* Latin and French are bad enough* for most of us, but how many readers possess a smattering of French provincial dialects? (Or couldn't the translator figure it out either?)

Louis Lasagna

*O. K., impossible.

CONCEPTS OF MEDICINE. Edited by Brandon Lush, M.D., M.R.C.P. New York, 1961, Pergamon Press, Ltd. Pp. 286. Price $8.50.

An interesting collection of essays by some distinguished British and American men of medicine has been put together by a Senior Medical Officer of the British Medical Research Council. Almost all the pieces concern the art or science of medicine in its broadest aspects. Most are by Britishers and reprinted from English periodicals (especially the *Lancet*). Dr. Lush obviously has some favorites: Out of a total of 26, Himsworth and Pickering have 4 papers each and Platt has 2. For this reviewer, the most stimulating essays were by Platt, Ryle, and Green, but all except a few seem well chosen.

Here are a few excerpts:

"I doubt if any professor of medicine should be more than fifty-five."

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"The spirit of research is to a university what morale is to an army."

"The conflict between the administrator and the educationalist is very similar to that between the farmer and the gardener, between the ready-made and the made-to-measure tailor."

"It often gives me some quiet satisfaction to realize that whatever you may think of yourselves biographically, biologically you are nothing but a lot of clones." [One wonders whether Platt thinks of his friends as old cronies.]

"Man's native curiosity atrophies by disuse. The reasons for the persistence of childlike curiosity into adult life in some individuals are quite unknown."

"There are no more rugged individualists in the world than a group of investigators in a medical school. They make the members of the National Association of Manufacturers look like so many ball bearings in a box."

"The man who decides to study for the rest of his life simply because he enjoys learning things and has a capacity for having intellectual adventures will do far better than another man who backs into academic life in search of what has been called by Cyril Connoly 'a womb with a view.' "

One small cavil: Why the hysterical attack by Walsh on ". . . that furtive and loathsome creature, the anonymous semen donor." Surely it is hyperbolic to label donors "a fitting symbol of the disintegration of Christian civilization." Come, now, sir!

Louis Lasagna

CLINICAL DISORDERS OF THE PULMONARY CIRCULATION. Edited by Raymond Daley, M.A., M.D., John F. Goodwin, M.D., and Robert E. Steiner, M.D. Boston, 1960, Little, Brown & Company. Pp. 364, indexed. Price $14.00.

Clinical Disorders of the Pulmonary Circulation by a distinugished group of British physicians provides an excellent review of cardiopulmonary physiology. There are chapters on anatomy of the pulmonary vasculature, hemodynamics, pulmonary function, pulmonary hypertension, radiologic aspects, pathology, electrocardiography, the effects of various forms of heart disease, the effects of various forms of pulmonary disease, and experimental pulmonary edema. Although it is impossible to publish a completely up-to-date textbook in a field which is progressing so rapidly, this book provides an excellent summary and critical review of data up to 1959.

In the generally excellent chapter on the effect of mitral valve and left atrial disease on pulmonary circulation, Dr. Goodwin makes the statement that left heart catheterization is rarely necessary except in particularly difficult cases. Much of his discussion of the hemodynamics is based on pulmonary capillary venous pressure measurements. The widespread use of the various techniques of left heart catheterization, and their unquestioned superiority over pulmonary capillary wedge pressures in accurate measurements of left atrial hemodynamics makes this statement seem a little old-fashioned for a textbook with a 1960 publication date. This is a minor criticism, and the chapter is quite well written and very informative. In a few cases, the illustrations appear to have been hastily assembled and the reproduction is of poor quality, but generally, the illustrations are adequate.

This book is of special importance to students of the cardiac or pulmonary physiology, and there is appropriate coverage of the various aspects of clinical management of cardiopulmonary disorders, so that the book will be of interest to the practicing physician as well.

J. M. Criley

EVALUATION AND MANAGEMENT OF THE BRAIN-DAMAGED PATIENT. By Jerome S. Tobis, M.D., and Milton Lowenthal, M.D. Springfield, Ill., 1960, Charles C Thomas, Publisher. Pp. 109, not indexed. Price $6.00.

In the care of patients with brain damage, the emphasis in the past has been primarily on diagnosis. This monograph attempts to shift the emphasis to evaluation and management in terms of what can be done to increase the patient's independence, once the diagnosis has been established. The book is simply written and illustrated. Hemiplegia, Parkinson's disease, cerebral palsy, and multiple sclerosis are considered in detail. It will be particularly helpful to physicians

unfamiliar with the techniques of physical medicine, as well as to nurses, physical therapists, speech therapists, and social workers.

Douglas Carroll

GRADUATED RECIPROCATION IN TENSION-REDUCTION. A KEY TO INITIATIVE IN FOREIGN POLICY. By Charles E. Osgood. Urbana, Illinois, 1960, The University of Illinois, Institute of Communications Research. Pp. 82, mimeographed.

Dr. Osgood is a respected psychologist who has been interested in the problems of disarmament for some time. The present monograph is a superbly written exposition of his "graduated reciprocation" plan for decreasing world tensions. It makes fascinating reading and should prove of interest to many. Osgood cannot be dismissed as an unrealistic idealist. His program seems more logical and "realistic" than those proposed by devotees of nuclear deterrence. Recommended reading for all those interested in self-preservation.

Louis Lasagna

SURGERY OF THE AORTA AND ITS BRANCHES. By James D. Hardy, M.S., M.D., F.A.C.S. Philadelphia and Montreal, 1960, J. B. Lippincott Company. Pp. 386, indexed.

This small book by Dr. Hardy is a combination of seven articles on various aspects of arterial disease which he had written for a medical journal. His style is lucid and reads well. The data presented emphasize general principles of diagnosis and management with the possibilities available by various therapeutic approaches. Details of surgical technique are not given. The few illustrations are appropriate and well constructed. The bibliography is extensive and recent and, as such, will be a good reference source on various aspects of arterial disease. I believe the book will be useful primarily to the medical student or to someone who has limited information about arterial disease. As such, it should be a good introduction to the subject.

Frank C. Spencer

BLOOD DISEASES OF INFANCY AND CHILDHOOD. By Carl H. Smith, M.A., M.D. St. Louis, 1960, The C. V. Mosby Company. Pp. 572, indexed. Price $17.00.

With the publication of this book, persons interested in blood diseases of infants and children now have available for the first time a comprehensive and instructive text. As Dr. Smith states in the preface, emphasis is placed on the "interpretation, diagnosis, and management of the blood diseases encountered in pediatric practice." Consequently, special consideration is given to the etiology and treatment of hyperbilirubinemia of the newborn, as well as other abnormalities of the blood which occur exclusively in the neonatal period. These chapters are especially valuable since many of the topics are too briefly presented in general textbooks of hematology.

The bibliography for each chapter is comprehensive, if not exhaustive, and most of the pertinent references in the recent literature are listed. Since the diagnostic and therapeutic aspects of the pediatric blood dyscrasias are emphasized, it is important to point out that Dr. Smith and his group have had extensive clinical experience in this field, and in many instances have contributed original observations relating to the clinical management of these problems. One minor criticism is the paucity of illustrations, notably the graphic presentation of relevant case histories. Future editions would be enhanced by the inclusion of this material.

This important book is highly recommended to all persons caring for children with hematologic diseases.

William H. Zinkham

Announcements

A two-year program of RESEARCH TRAINING IN PSYCHIATRY leading to the degree of Doctor of Medical Science is offered by the Graduate Educational Program of the State University of New York Downstate Medical Center. The program is open to M.D.'s who have completed three years of residency training in psychiatry. Candidates who have completed two years of residency will also be accepted. In such cases the final year of residency will be taken at the Psychiatric Division of Kings County Hospital concurrently with this program; and a total of three years will be required to complete the combination of the two-year training program and the third year of residency.

The program provides the candidate an opportunity to do research, and it offers a series of courses concerned with research methodology and current major concepts in the field of psychiatry. A broad interdisciplinary faculty is responsible for teaching courses in the curriculum and for supervising research of candidates. Extensive clinical and laboratory facilities are available for research projects.

Each candidate accepted into the program will be granted a fellowship of $6,000 for the first post-residency year and $7,000 for the second post-residency year. These fellowships may be supplemented by stipends for special research or teaching. Three-year candidates will receive $7,100 for the final residency year. Applications for the academic year beginning September, 1962, should be submitted before Feb. 1, 1962.

Application forms or additional information about this program may be obtained by writing to: Office of Admissions, Downstate Medical Center, 450 Clarkson Avenue, Brooklyn 3, N. Y.

THE AMERICAN UROLOGICAL ASSOCIATION offers an annual award of $1,000 (first prize of $500; second prize, $300; and third prize, $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been graduated not more than ten years, and to hospital interns and residents doing clinical or laboratory research work in urology. Animal research is not necessary.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Bellevue-Stratford Hotel, Philadelphia, Pa., May 14-17, 1962.

For complete information write to: William P. Didusch, Executive Secretary, 1120 North Charles Street, Baltimore 1, Md. Essays must be in his hands before Nov. 15, 1961.

The ELEVENTH ANNUAL INSTRUMENT SYMPOSIUM AND RESEARCH EQUIPMENT EXHIBIT will be held on Oct. 9 to 12, 1961, at the National Institutes of Health, Bethesda 14, Md.

Primary topics for discussion on the scientific program include: (1) Applied Gas Chromatography; (2) Factors Influencing Interpretation of Spectra; (3) Electron Magnetic Resonance; (4) Thermogravimetric Analysis; (5) Electron Probe Analysis; (6) Application of Physiological Instrumentation to Clinical Problems; and (7) Optical Rotatory Dispersion.

Examples of the latest types of research equipment will be exhibited by instrument manufacturers.

For further information contact Mr. James B. Davies, National Institutes of Health, Bethesda 14, Md. (Phone: OLiver 6-4000, Ext. 2315.)

The Department of Physical Medicine and Rehabilitation of the New York Medical College will conduct a one-week course for physicians only in "REHABILITATION CARE OF THE CHRONICALLY ILL PATIENT" from Nov. 13 to 17, 1961.

This course for physicians is planned to provide a broad review of the principles, techniques, and problems involved in the medical rehabilitation of the chronically ill and has been developed with the intent of meeting such needs for the clinician, medical administrator, and public health physician. The course will consist of lectures, seminars, and clinical demonstrations. The teaching staff includes members of the faculty of the medical college, noted guest lecturers, and members of the clinical staff of the hospital center.

The curriculum includes:

- Physiology and Pathology of Chronic Disease
- Nutrition and Dental Care
- Home-Care Programming
- Community Needs and Resources
- Public Health Aspects
- Management Problems of:
  - The Bedridden Patient
  - The Incontinent Patient
- Self-Care Activities
- Prosthetic Devices
- Psychological and Social Aspect

The curriculum material will be related to such neuromuscular and musculoskeletal conditions as hemiplegia, arthritis, multiple sclerosis, parkinsonism, cerebral palsy, hip fractures, amputations, muscular dystrophy, and paraplegia. Tuition will be $150.

Further information may be obtained from: Mr. Raymond C. Lerner, M.S.S.W., Coordinator—Postgraduate Education, Department of Physical Medicine and Rehabilitation, New York Medical College, 1 East 105th Street, New York 29, N. Y.

A WINE RESEARCH AWARD has been established by the Society of Medical Friends of Wine to stimulate additional research into the uses of wine in medicine.

The award of $1,000 is offered to individuals or institutions who have conducted and published original research of conspicuous value in one of the following respects: (1) in identifying substances in wine, (2) in ascertaining the effects of components of wine on living cells, tissues, or organs, or (3) in indicating appropriate clinical applications of wine in the treatment or prevention of disease.

The Society's Research Committee, of which Hilliard J. Katz, M.D., of 450 Sutter Street, San Francisco, Calif., is chairman, will consider outstanding contributions and nominate possible recipients. The final selection will be determined by the Society's membership and its Board of Governors.

The International Society for Rehabilitation of the Disabled has announced the availability of REHABILITATION AND WORLD PEACE—PROCEEDINGS OF THE EIGHTH WORLD CONGRESS OF THE INTERNATIONAL SOCIETY. This work represents the latest addition to the Society's ever-expanding library of rehabilitation literature.

Rehabilitation and World Peace, a comprehensive report of the many general and special sessions held during the Congress, also contains lectures and special papers submitted by the world's most eminent rehabilitation specialists. The unprecedented attention which was given to this world meeting sparked an advance sale of over ten thousand copies of the Proceedings. The Congress was attended by more than 3,000 persons from eighty countries of the world.

Copies of *Rehabilitation and World Peace* are available from the International Society for Rehabilitation of the Disabled, 701 First Avenue, New York 17, N. Y. at the price of $1.00 per copy. Special discounts are being offered on orders of 100 or more copies.